Diabetes of Anterior Pituitary and Adrenal Cortical Origin

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In recent years it has become increasingly clear that diabetes mellitus, once considered a disease entity, must in the future be looked upon as a group of diseases which have one common feature—hyperglycemia. Disorders which cause hyperglycemia vary greatly and in essential ways. Although it is possible in some instances to point to reversal of diabetes to a state of cure even after it has persisted for a long time, it must also be recognized that long-sustained hyperglycemia, regardless of its cause, may in itself be sufficient in some individuals to precipitate lasting pancreatic diabetes. The various forms of diabetes which are emerging most clearly (to be added to pure beta cell failure) include pituitary diabetes due to excess of growth hormone, diabetes due to excess of corticotropin (ACTH), and diabetes due to excess of adrenocortical steroids of the 11-oxysteroid type.

ANTERIOR PITUITARY DEFICIENCY AND DIABETES

It is now thirty years since Olmsted and Logan[1] at the University of Toronto called attention to the fact that pituitary activity had a striking influence on the effectiveness of insulin. They showed that insulin convulsions could be induced in decerebrated cats whose pituitaries were removed, but not in similar animals given the same dose of insulin if the pituitaries were intact. The classical experiments of Houssay[2] demonstrated clearly the marked amelioration of pancreatic diabetes which follows pituitary ablation in animals.

In the human being, severe anterior pituitary failure superimposed on diabetes is very rare, but there are at least eight cases in the literature in which this has followed disease processes. Four such patients, with an added one of his own, were cited by Feldman and his associates[3] in 1947. More recently reported instances are those of Marzullo,[4] Poulsen,[5] and Williams.[6] It is remarkable that although the general effects of Simmonds' disease were severe in all of these, the effects on the pre-existing diabetes differed markedly. In Calder's[7] patient a glucose tolerance test previously diabetic in type became normal, and in Vandenbroeck and Ferin's[8] patient the insulin dose fell from 60 to 43 units per day. At the other extreme, Kotte and Vonderahe's[9] patient, who had acute pituitary necrosis, had previously had "excessive glycosuria," which disappeared in two days after pituitary destruction, and the blood sugar level fell to 31 and finally 20 mg. per 100 cc. Feldman's patient had taken 35 units of insulin daily, but as pituitary cachexia developed this was discontinued and she died in hypoglycemic crisis. Similarly, Williams' patient had required 60 units of insulin per day, yet after pituitary necrosis she died following hypoglycemic crisis despite 60 gm. of intravenous glucose.

The extreme sensitivity to injected insulin in the presence of anterior pituitary deficiency is well-known clinically and is dramatically illustrated by the report of Horstmann.[10] His patient also had severe hypopituitarism. During investigation she was given a test dose of eight units of insulin intravenously. She developed hypoglycemic coma and died despite the use of glucose intravenously.

HYPERGLYCEMIA FOLLOWING THE ADMINISTRATION OF PITUITARY EXTRACTS

More than twenty years have elapsed since Houssay[11] demonstrated that hyperglycemia and glycosuria followed the injection of crude pituitary extract into normal animals. His findings were soon amply corroborated.[12, 13]

Over 15 years ago, Young[14] produced the first permanent diabetes in normal dogs by daily intraperitoneal injection of crude, ox, anterior pituitary extracts. Continued work along these lines has strengthened the belief that such diabetes is due to the effects of growth hormone.[15]

There is also strong evidence that the permanence of such diabetes is intimately connected with degeneration of the beta cells of the pancreas, as has been shown microscopically, and by the fact that such diabetes does not develop or can be reversed if hyperglycemia is overcome with insulin;[16] or, as Lukens, Dohan, and Wolcott[17]

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found in cats, it can be reversed if the hyperglycemia is prevented by exaggerating urinary loss of sugar through phlorizin treatment. It is interesting to remember that whatever the relationship of this diabetes to the pancreas, it tends to require more insulin for its control than pure pancreatic diabetes produced surgically.

In this connection there are two pieces of evidence which seem to be conflicting and should be correlated. On the one hand, Young causes permanent diabetes in intact cats with Li's or Wilhelmi's growth hormone preparation in doses of 1 mg. per kg. per day and in dogs with 2 mg. per kg. per day. On the other hand, Houssay[21] finds that 25 times that dose is required in partially depancreatized dogs and cats. Does the hyperglycemic factor play an important role?

Whether growth hormone is itself diabetogenic or whether this property is associated with some impurity of the preparation is not fully settled. The possibility of corticotropin contamination has been considered. It is interesting in this connection that both Houssay and Anderson[18] and Campbell and others[19] failed to produce definite diabetes in the dog and cat with corticotropin, yet it can be readily produced by growth hormone.

At present, the balance of evidence seems to favor the belief that growth hormone has diabetogenic power. Considerable doubt was cast on this two years ago, when Raben and Westermeyer[20] presented evidence that their preparation could produce growth in rats without influencing the blood sugar level. This work, however, has not been confirmed. Young[21] observed that the stronger the growth-producing properties in pituitary extracts, the more marked are the diabetogenic effects.

Reid[22] has produced two interesting sets of facts bearing on this part of the problem. First, treatment of growth hormone by various agents, including acid, enzymes, iodination, and acetylation, causes a disappearance of growth and of diabetogenic effects at parallel rates. Second, growth-promoting and diabetogenic effect both appear to depend on the integrity of the epsilon-amino acid groups of the lysine residues in the peptide chain, and not on the alpha-amino acid groups of the alanine and phenylalanine residues at the ends of the chains.

ACROMEGALY AND DIABETES

The diabetes of acromegaly is the clinical counterpart of the type of diabetes under discussion. In a given case, it is not possible to state with certainty whether growth hormone excess is the sole factor or whether some excess of corticotropin with incident excess of oxysteroids is also involved. Most critical observers are not satisfied with the reliability of methods currently available for the estimation of excesses of 11-oxysteroids, and the methods most recently developed have not yet been fully evaluated in acromegaly. It is to be hoped that such new methods as that of Sydnor and Sayers[23] for blood corticotropin will help to solve this part of the problem.

It is true that large adrenal cortices have been found commonly in acromegaly, and Venning and Browne[24] found that increased excretion of corticosteroids may occur. If in acromegaly excess corticotropin is produced, one would expect the frequent development of Cushing's syndrome, just as it should occur theoretically in pheochromocytoma because of constant adrenalin stimulation to corticotropin production. Acromegaly and Cushing's syndrome rarely coexist. One such case is that reported by McCormick and his associates.[25] In this patient there was apparently an excess of corticotropin. (Assays for this hormone were done in this case by Dr. A. Albert.) Daughaday, Perry, and MacBryde[26] demonstrated an increase in urinary "cortin" by the formaldehydogenic method in their insulin resistant case.

The incidence of diabetes in acromegaly has been variously reported. The most frequently quoted figure is that of Coggeshall and Root,[27] who found in 153 acromegalic patients 35 per cent with glycosuria and 17 per cent with diabetes. It seems fair to assume that many more than 17 per cent might be classed as diabetic if glucose tolerance tests were done in all cases. It may be pertinent, however, that corticotropin and cortisone cause glycosuria before hyperglycemia occurs as a result of their action on the kidney.[28] With the experimental facts in mind it is not easy to understand why so relatively few patients with acromegaly have diabetes.

The time relationship between the beginning evidence of acromegaly and of diabetes varies tremendously according to available figures. Coggeshall and Root's analysis shows a variability of one to twenty-two years, and the figures of Goldberg and Lisser[29] are similar. In one of our cases, diabetes and acromegaly were present together when the diagnosis was first made; in another the acromegaly was known to have been present for fifteen years before diabetes was found. In the remainder the time interval between the beginning of acromegaly and of diabetes apparently lay between these extremes.

In 76 acromegalic patients in our series, 21 were classified as diabetic. It seems evident that mild diabetes, which is disclosed only if a glucose tolerance test is done, is present in many such patients and for an unknown

length of time before it is demonstrated.

Diabetes is said to occur much more frequently in women with acromegaly than in women generally. In our series there were 9 women and 12 men. In Coggeshall and Root's[27] series the incidence of diabetes was also much higher in the acromegalic patients with a family history of diabetes.

While most acromegalic diabetes is mild, it is sometimes severe. In 3 of Root's 16 fatal cases, for example, the patients died in diabetic coma. Insulin resistance occurs, and it is a common impression that it occurs more frequently in acromegalic diabetics than in the average diabetic. With this we agree, but we cannot support our opinion with accurate statistics. We have one acromegalic patient, a man of 48 years, who requires 160 units of insulin per day for maintenance. There are two others who have required 220 and 175 units daily, respectively, for brief intervals but usually require doses ranging around 60 and 80 units.

The muscle wasting and the signs simulating amyotrophic lateral sclerosis do not parallel the severity of diabetes in acromegaly. The muscle weakness may be extreme, or actual amyotrophic lateral sclerosis may be present with very mild or no diabetes, or diabetes may be severe with no evident muscle wasting or weakness.

Arterial hypertension, arteriosclerosis, and intracranial vascular accidents are common in acromegaly. Diabetic retinopathy has also been reported.[27] We have seen typical diabetic retinopathy in 3 of 21 acromegalic diabetics. One was a man who had had acromegaly for twelve years and diabetes for eight years when retinal changes were first seen. His blood pressure was 160/100. In another case, a few punctate hemorrhages were found in a man known to have had diabetes for only two years. His blood pressure was 110/60. The third patient was a 28-year-old man who had actively recurring retinal hemorrhages. He had been known to have had acromegaly for ten years. He had had improvement in visual fields and apparent slowing of acral growth after operation on a pituitary tumor in 1944. Despite this he developed diabetes two years later, which was five years before retinopathy was found. His blood pressure was 120/90.

Neither coma nor gangrene has been seen in any of our acromegalic patients. The type of renal failure noted in chronic diabetes, if present, has not been recognized by us in our acromegalic patients. The paucity of such vascular complications may be related to the fact that most of these patients die before their disease has lasted fifteen years, which usually means that the diabetes has existed for a much shorter time.

An unusual variability in the severity of diabetes of acromegaly is mentioned frequently in the literature. In a sense this is true, but in watching the progress of acromegaly for years we have been more impressed with the fact that the diabetes is usually mild and peculiarly stable—vastly different in this respect from that of so many cases in which we struggle daily to try to attain diabetic control. It is equally true, however, that diabetes may show ingravescence during maintained pituitary hyperfunction and slow or sudden amelioration with decline in hypophysial function. However, Darragh and Shaw[30] reported the development of diabetes in acromegalic patients in spite of the apparent arrest of the acromegaly following x-ray treatment of the pituitary.

The case of Almy and Shorr[31] is most instructive. A 40-year-old acromegalic patient with diabetes for five years developed mastoiditis and basilar meningitis. He had required 60 units of insulin per day. Later, associated with evidence of pituitary failure, his glucose tolerance became normal and remained so for five years. In John's[32] case there was spontaneous disappearance of diabetes in a patient with acromegaly. Balfour and Sprague[33] had a somewhat similar experience. Their acromegalic patient who had had blood sugar levels as high as 384 and required 62 units of insulin daily, following x-ray therapy had an acute episode thought to be due to rupture of an intrasellar tumor. Later, 10 units of insulin daily kept the blood sugar at a level of 147 mg.

In our own experience,[34] reversal of diabetes has followed long-continued therapy with estrogen. A report of this experience refers to 6 patients, 5 of whom had mild diabetes as shown by abnormal glucose tolerance tests. The doses of estrogen used were relatively large. Stilbestrol was given in doses of 10 to as much as 50 mg. per day or ethinyl estradiol 1.0 to 5.0 mg. per day, which is twenty to one hundred times the usual dose. The changes took months to occur. Although the patients were not on carefully regulated diets, we believe that the changes are significant because they were progressive and were consistent in all five cases. In addition, after the glucose tolerance became normal or nearly normal during therapy, cessation of treatment was followed in 3 cases by a recurrence of the abnormal glucose tolerance test. Growth hormone production was apparently suppressed because there was shrinkage of soft tissue and a sustained lowering of blood phosphorus levels. The change in glucose tolerance, we believe, was due in part at least to diminished growth hormone production.

DIABETES MELLITUS AND ADDISON'S DISEASE

The amelioration of diabetes by adrenalectomy or in Addison's disease is a familiar story. Existing diabetes can be controlled on much less insulin than before adrenal deficiency, and such patients are extremely insulin-sensitive, yet it is peculiar that between hypoglycemic episodes, blood sugar levels may rise rapidly to higher than 400 mg. per 100 cc.

In patients with Addison's disease and diabetes, insulin reactions are severe and dangerous. In one of our patients a hypoglycemic convulsion which occurred in bed was so severe that it caused dislocation of the head of the humerus. In one of the cases reported by Balfour and Sprague,[33] insulin reactions followed 3 units of insulin. The blood sugar level varied from 40 to 492 mg. After treatment with cortisone there was marked glycosuria, high blood sugar level, ketonuria, high urinary nitrogen, and a rise in insulin requirement to 44 units, which was almost exactly the dose used prior to the onset of Addison's disease. In Green's[35] case, in which adrenalectomy was done for malignant hypertension, approximately 20 units of insulin was still required to control the diabetes.

Although not much insulin is tolerated, yet in some ways the diabetes retains its former severity. In one of Sprague's cases, there was glycosuria graded 4-plus and a blood sugar of 289 mg. in the face of frank Addison's disease. This patient after having received cortisone and then having it withdrawn developed severe ketosis in nine hours.

CORTICOTROPIN, 11-OXYSTEROIDS, AND DIABETES MELLITUS

The effects of corticotropin and cortisone in relation to diabetes can be considered together. One may first recall some of the outstanding biochemical effects of these compounds. Later the administration of these hormones in human diabetes will be considered and finally some features of the diabetes seen in Cushing's syndrome will be noted.

One of the most outstanding actions of cortisone-like hormones is their ability to cause deposition of glycogen in the liver. The various hormones possess this ability in the following descending order: hydrocortisone, cortisone, corticosterone, and 11-dehydrocorticosterone. Continued injection of corticotropin or cortisone is not followed by persisting high levels of liver glycogen, however, for these decrease to normal after a few days.

Cortisone controls the fasting hypoglycemia of adrenal failure. It causes a rise in blood and tissue carbohydrate, which is paralleled by a rise in the excretion of nonprotein nitrogen. This has led to the hypothesis that the sugar arises from gluconeogenesis, but Ingle[36] has demonstrated clearly that the severe glycosuria induced in normal animals by these compounds is much too great to be accounted for on the basis of the glucose derived from protein breakdown.

Although the weakness caused by adrenalectomy is associated with hypoglycemia, this is not a cause-and-effect relation since continuous intravenous infusion of glucose improves only slightly the ability for muscle work of adrenalectomized animals.[37] Certain other features of the actions of these hormones may have a close relationship to the "steroid diabetes" which they can cause. They cause an increase in uric acid excretion.[38] It has been suggested that the production of an "alloxan-like" metabolite from the pyrimidine portion of the nucleic acids may lead in turn to damage of the beta cells, either directly or perhaps secondarily by reducing blood glutathione. In the experimental animal[39] these hormones reduce the level of blood glutathione, and these substances in turn have a powerful effect in preventing beta cell degeneration from diabetogenic stimuli.[40] It has been claimed that a similar role of glutathione could be shown in the human being,[41] but this is controversial.

In earlier work carried out in a very small number of subjects, glutathione values did not seem markedly abnormal. Furthermore, the methods used for glutathione determinations were not specific and hematocrit corrections were not taken into consideration.

One of us (J. A.)* found no significant changes in blood nonprotein sulfhydril levels when 100 mg. of hydrocortisone was administered in short-term experiments, despite a carbohydrate intolerance, shown by a glucose tolerance test at the end of the infusion. The hormone was administered intravenously for six hours to three normal subjects and the results were compared to those obtained during control infusion (5 per cent dextrose plus 1 per cent alcohol) in the same individuals.

It has also been suggested that corticotropin may stimulate the alpha cells to produce glucagon.[43]

Many must have wondered what the connection is between potassium and carbohydrate on the one hand and potassium and the adrenal on the other. Verzar[44] calls attention to the following facts observed in normal animals: (1) In muscle contraction when glycogen is

*Unpublished data derived from work done at McGill University Clinic, Montreal. Nonprotein sulfhydril was determined by the amperometric titration method as modified by Goldzieher and associates[42] and corrections were done for hematocrit values.

broken down, potassium is set free. (2) Intravenous injection of glucose leads to hyperglycemia and a rise in blood potassium. (3) After intravenous adrenalin, blood sugar and blood potassium levels both rise. (4) None of these effects occurs after adrenalectomy. Clinically it appears that the direction of blood potassium shift may not be upwards.

In the human being, Wilson, Frawley and Forsham[45] have reported that a fall in serum potassium concentration occurs during the intravenous glucose tolerance test in diabetic patients as in nondiabetics who are under treatment with corticotropin. Similar findings have been observed in patients with Cushing's syndrome in spite of the presence of a normal glucose tolerance test. These studies point to the existence of certain metabolic phenomena similar to those seen in diabetes even though no other obvious manifestations (hyperglycemia, abnormal glucose tolerance test) of diabetes are present.

Verzar[46] has reviewed the influence of adrenal cortical hormones on enzyme systems. Although the action of cortisone has not been closely identified with any specific enzyme system, it has been suggested that phosphorylase may be involved.

Corticotropin and cortisone given in the usual therapeutic doses seldom have enough effect on the blood sugar to be of clinical significance (figure 1). As has been

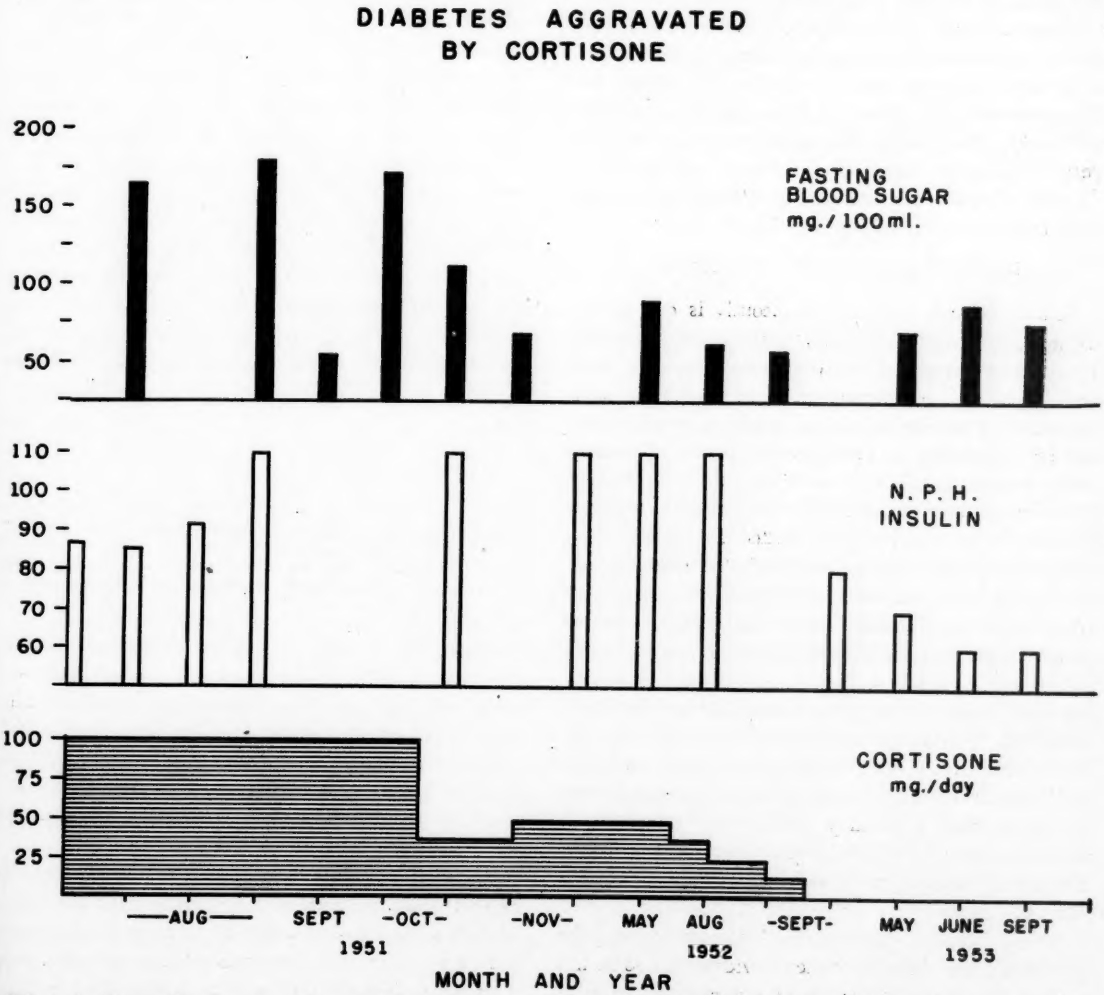

FIG. 1. A 50-year-old man was given cortisone for severe rheumatoid arthritis. In the doses shown, his insulin requirement increased about 25 units per day. There was no lasting aggravation of the diabetes.

stated, cortisone may cause marked aggravation of diabetes if present in Addison's disease, and it probably would do the same to some degree in Simmonds' disease. In an occasional susceptible individual, the diabetes is precipitated or unrecognized diabetes is aggravated. For example, in Fajans'[47] case under treatment with corticotropin because of leukemia there was great intensification of the diabetes. There was glycosuria to as much as 100 gm. per day over dietary intake, 23 gm. negative nitrogen balance, and insulin resistance.

It can be confidently anticipated that diabetes existing in latent form may remain severe in some people after it has been made severe by steroid effects. Fortunately, such must be the case very seldom.

Bookman[48] cites 5 cases in which diabetes developed during cortisone or corticotropin therapy. It disappeared in 4 cases. The other patient probably had diabetes before treatment since there had been glycosuria ten years previously. This patient was given cortisone for two years—usually 75 mg. daily—and now requires 10 to 20 units of insulin per day. Lasting diabetes may actually have been caused in Bishop and Glyn's case.[49]

DIABETES OF CUSHING'S SYNDROME

Steroid diabetes arising spontaneously is due to 11-oxysteroid-like materials. They cause glycosuria partly by an effect directly on the renal tubules and they cause both glycosuria and hyperglycemia by interfering with the action of insulin, impairing carbohydrate utilization, and by augmenting the breakdown of protein. Clinically such diabetes is relatively mild and relatively insulin insensitive; it may be associated with a negative nitrogen balance which is not fully corrected by insulin. It is usually temporary, disappearing with the correction of the steroid excess on which it depends. It occurs in its typical form in Cushing's syndrome, which is due to adrenal hyperplasia or adreno-cortical tumors, and more rarely due to pituitary tumors. In patients with this syndrome, adrenal hyperplasia accounts for approximately two-thirds of the cases and adrenal tumor for approximately one-third. In the rare instance in which Cushing's syndrome or Cushing's disease is caused by excessive corticotropin from a pituitary tumor, x-ray treatment of the tumor may bring about improvement. In the others, removal of about 80 per cent of adrenal tissue leads to complete control.

Severe Cushing's syndrome of long standing may be present without diabetes. It seems evident that some important homeostatic mechanisms come into play. In some cases, steroid diabetes is associated with hypokalemic hypochloremic alkalosis. This was true in the case reported by Sprague and his associates,[50] in which relatively large amounts of 17-hydroxycorticosterone were isolated from the urine. Patients with a combination of Cushing's syndrome and adrenogenital syndrome may also have diabetes. We have seen one case of apparently pure adrenogenital syndrome in which severe alkalosis was present but diabetes was absent. The relative rate of appearance of diabetes in Cushing's syndrome and the degree of improvement in glucose tolerance following successful adrenal surgery are indicated in figure 2.

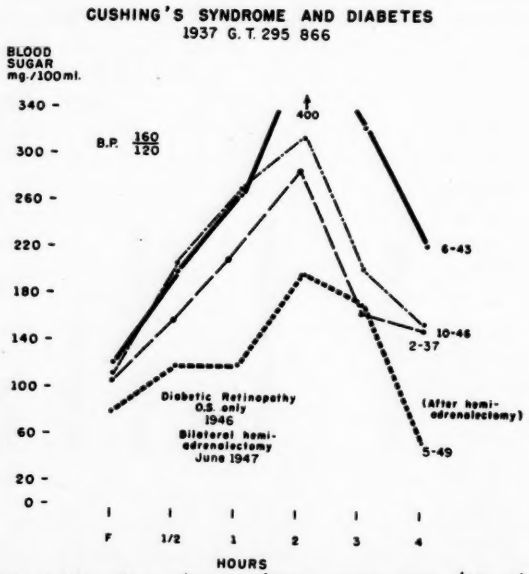

FIG. 2. The above glucose tolerance curves were done at intervals during ten years before successful surgery and two years following disappearance of Cushing's syndrome after removal of approximately 80 per cent of the adrenal tissue.

Among our 34 cases of Cushing's syndrome, diabetes was present in 21, 15 women and 6 men. Insulin was prescribed in 7 cases. The lowest daily dose of insulin was 8 units and the highest dose was 90 units. Vascular complication usually associated with hypertension is almost an integral part of Cushing's syndrome, and consequently one cannot always be sure how much of the vascular disease is of diabetic origin.

Three patients in our series had retinopathy. In one of these there was a hemorrhagic retinopathy not typical of diabetes in a patient with a blood pressure of approximately 175/120. The other two patients had retinopathy classified as diabetic. One of these patients had had features of Cushing's syndrome for eleven years and dia-

betes for nine years before the retinopathy was found. In the other patient the blood pressure had been as high as 196/128; the diagnosis of Cushing's syndrome and diabetes was made in 1936 and the retinopathy was discovered eight years later.

The possibility that certain chemical features of the diabetes in Cushing's syndrome are different from those in the usual case of clinical diabetes has been studied by Hills, Power, and Wilder.[51] In 34 patients with mild diabetes the blood lactate and pyruvate levels were nearly normal. Of six patients with Cushing's syndrome and diabetes mellitus, four had pyruvate and lactate which were markedly elevated before glucose was given for a glucose tolerance test and even more elevated after the giving of glucose, differing in this way from patients with mild diabetes without Cushing's syndrome; among the six patients with Cushing's syndrome and diabetes who were studied, the other two had hypokalemic hypochloremic alkalosis.

In steroid diabetes of long standing there may be no tendency to permanence of the diabetic state. When postoperative adrenal insufficiency arose in the patient whose curves are shown in figure 3, not only did the diabetes disappear but the tolerance became that typical of Addison's disease. It is an interesting fact, however, that both our patients with severe Cushing's syndrome, who had complete clinical recovery following adrenal surgery, suffered severe myocardial infarction ten years later.

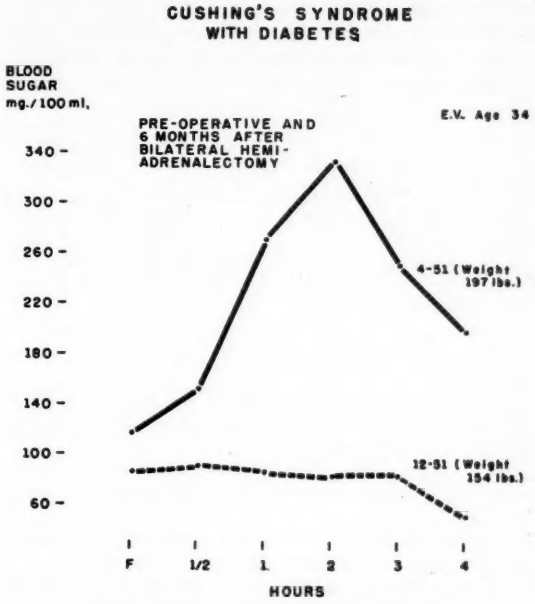

FIG. 3. Cushing's syndrome had been present for at least four years when adrenal deficiency developed post-operatively. The diabetes which had been present was replaced by the flat type of glucose tolerance curve commonly seen in Addison's disease. The loss of 43 pounds may have played a part in this result.

SUMMARY AND CONCLUSIONS

The relationship of diabetes to disease of the anterior pituitary and adrenal cortex is reviewed chiefly from a clinical standpoint and some of the pertinent experimental evidence is outlined. The pituitary aspects are considered in relationship to: (1) pituitary failure superimposed on diabetes; (2) hyperglycemia following the use of pituitary extracts, especially growth hormone; and (3) acromegaly and diabetes.

With regard to growth hormone, most of the evidence implicates this hormone itself as the specific diabetogenic factor, although there is some evidence to the contrary. In acromegaly, although diabetes occurs frequently, it is also true that it may be absent. When present it is usually mild. The fact that severe acromegaly may exist without diabetes seems to us to be an argument against the possibility that growth hormone is a factor of fundamental importance in diabetes as usually seen clinically.

The subject of the adrenal cortex and diabetes is reviewed under the following subtitles: (1) diabetes mellitus and Addison's disease; (2) the relationship of corticotropin and 11-oxysteroid administration to "steroid" diabetes (here some of the mechanisms proposed to explain the diabetogenic effects of these hormones are discussed and the possible danger of causing lasting clinical diabetes is mentioned); and (3) diabetes and Cushing's syndrome. It is noted that many patients with Cushing's syndrome have diabetes, but some escape even though other manifestations of the disease are severe and of long standing. Some of the peculiarities of steroid diabetes are mentioned, among which is evidence of chemical differences between steroid and other clinical diabetes. We consider it of interest that it has not been shown that the steroid diabetes of Cushing's syndrome causes diabetic retinopathy more frequently than other types of diabetes. This may be partially attributable to the fact that in most patients with the diabetes of Cushing's syndrome the diabetes had not been of as long duration as it has been in most patients with retino-

pathy without Cushing's syndrome. Because the "cure" of Cushing's syndrome is almost always followed by disappearance of the diabetes, we believe it unlikely that adrenal cortical hyperfunction is a common cause of diabetes mellitus.

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Who Discovered Vitamins?

Every writer who has given an account of the earliest conception that essential nutrients for mammals, other than the "albuminous, saccharine, and oleaginous principles" comprehended in 1827 by Prout, states that N. Lunin in 1880, while working in the laboratory of G. v. Bunge, at Dorpat, was the first to provide proof that unidentified dietary essentials must exist in milk.

The present writer believes that the first person actually to express this belief was the distinguished French chemist, J. A. B. Dumas. Ten years before Lunin, Dumas published a paper on "The Constitution of Blood and Milk," which was published in English translation in 1871. In this paper he described the effects of substitute foods on the infants of Paris during the Siege. Here, for the first time in history, a distinguished scientist interpreted his observations on the experiences of human subjects, restricted through the pressure arising from the siege, to a diet as simplified, in chemical terms, as any rigidly controlled animal experiment. Dumas told of the extremity of the people in Paris when they ran out of "comestibles and combustibles." He said ". . . to the scarcity of milk and eggs, the certain cause of the premature decease of a great number of young children . . . and finally, to the exhaustion of the supplies of corn, flour and meat, which, rendering the capitulation of Paris inevitable, marked the precise day for it. . . . Scientific men were asked urgently to find ways for obtaining heat without combustibles; to reconstruct food with mineral materials, without the cooperation of life . . . to reproduce, at least the essential food of man with nonalimentary materials.

"Was it possible," he continued, "to come to the assistance of newborn children by replacing milk, which could no longer be got, by some saccharine emulsion?"

The disastrous effects of feeding infants and young children on such emulsions led Dumas to say: "For these reasons, and many more, for no conscientious chemist can assert that the analysis of milk has made known the products necessary to the life which that aliment contains, we must renounce for the present, the pretensions to make milk, and especially to abstain from identifying any emulsion with this product."

So far as I am aware, the observations of Dumas appear never to have been mentioned by investigators of nutrition. They deserve recognition as the earliest conclusive demonstration that unrecognized nutrients exist, which before had found no place in the philosophy of physiologists and chemists.

From a letter by E. V. McCollum, M.D., in *Science*, Nov. 20, 1953.

Hypophysectomy in Human Diabetes

Metabolic and Clinical Observations in Diabetics with Malignant Vascular Disease

Laurance W. Kinsell, M.D., Lester Lawrence, M.D., Harry E. Balch, M.D., and Robert D. Weyand, M.D., Oakland, California

In discussing the diabetic child White[1] states: "Prior to 1922, the duration of life was 1.6 years. In 1922, insulin abolished lethal coma so that between 1930 and 1936, the duration of life increased to 7 years. Then antibiotic and chemotherapeutic agents controlled lethal sepsis and tuberculosis, with the result that today the juvenile diabetic is expected to survive more than 20 years." Elsewhere in her excellent paper she says that the vascular lesions make their appearance between the fifth and fifteenth years of duration.

As is well-known, Dr. Joslin and all his associates believe that the tendency to vascular disease in the juvenile diabetic can be lessened or even prevented by proper dietary management. Other eminent diabetologists feel otherwise. Whatever the final word on this may be, all physicians who see young diabetics are confronted with the hard fact that many of them, by the grace of insulin and antibiotics, have hurdled acidosis and infection only to reach a terrifying world of increasing blindness, renal insufficiency, and eventually a renal or a cardiac death. We believe that this represents one of the great challenges in the field of clinical investigation.

Clinical diabetes, from an endocrine standpoint, can be considered to be the resultant of relative or absolute lack of the hypoglycemic factor, insulin, on the one hand, and relative or absolute excess of pituitary, adrenal, and possibly other hyperglycemic hormonal factors, on the other (figure 1). The insulin requirement of a diabetic with simple insulin-lack should be essentially identical with that of the pancreatectomized individual. The juvenile diabetic admittedly requires much more than this amount of insulin, and hence must be considered to have not only partial or complete insulin-lack but also an absolute excess of factors with a hyperglycemic effect.

The mechanism of production and progression of the vascular disease so characteristic of the juvenile diabetic is far from clear. Probably the constant disturbance of intracellular and extracellular osmotic relationships, resulting from extreme blood sugar fluctuation over a period of months and years, is a major factor. The vascular damage associated with Cushing's syndrome and the vascular changes produced in diabetic animals by corticoid administration[2] suggest that chronic adrenal hyperfunction resulting from, or associated with, poorly controlled diabetes has a direct etiologic relation to the vascular damage. It is probable that both groups of factors play a significant part. If this be true, then a therapeutic approach designed to prevent vascular changes, or to ameliorate existing vascular damage, would have as its primary objectives stabilization of the diabetes, that is, maintenance of the blood sugar within the normal range, and elimination of excess production of adrenal steroids. Ideally such a result would be producible by dietary and hormonal treatment. At the present time, this is impossible or impractical in a significant number of juveniles with severe diabetes.*

Lacking adequate hormonal or other pharmacologic agents, a more drastic therapeutic approach must be considered, namely adrenalectomy or hypophysectomy. The potential assets and liabilities of such procedures were considered by us for some years. The decision to undertake hypophysectomy was finally made on the basis of our experience with several juvenile diabetics, all of whom had well established vascular disease when they first came to us. Following are abstracts of the progress of two such patients, both of whom were studied extensively on the metabolic ward.

Presented at the Annual Meeting of the American Diabetes Association in San Francisco on June 19, 1954.

From the Departments of Medicine and Neurosurgery, Samuel Merritt Hospital and the Institute for Metabolic Research of the Highland Alameda County Hospital, Oakland, Calif.

This work has been supported in part by grants from the National Institutes of Health, The Armour Laboratories, Merck & Company, Inc., and the Alameda County Heart Association.

*Preliminary studies in this laboratory with β-hydroxyprogesterone suggest that this compound may have some usefulness in this connection.

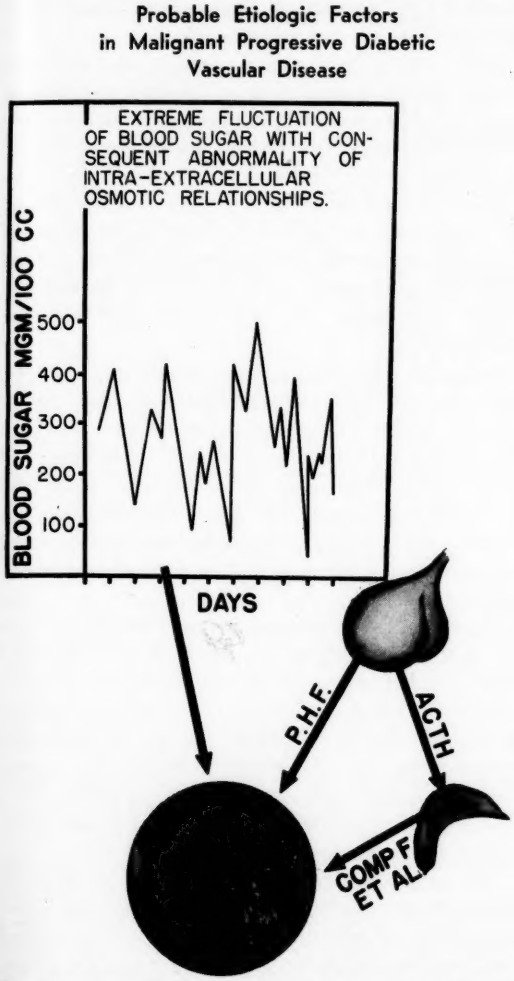

FIG. 1. Poorly controlled diabetes, adrenal cortical hormones, and pituitary hyperglycemic factor (PHF) may all play a part in the production of malignant progress in diabetic vascular disease.

PROGRESSION OF VASCULAR DISEASE—ILLUSTRATIVE CASES

Patient D.I.D., a 28-year-old man, was first admitted to the metabolic ward in February 1952. Diabetes had been diagnosed at the age of eight. In the five years prior to admission the average insulin requirement on a not too constant, relatively high carbohydrate diet averaged more than 80 units per day. Control had never been good, as evidenced by numerous hospital admissions for treatment of acidosis.

Clinical vascular disease first became apparent in 1950 or before; since that time there had been progressive impairment in visual acuity. The exact date of appearance of albuminuria is unknown, but manifestations of the nephrotic syndrome first appeared in 1952. The urinary albumin while the patient was on the metabolic ward averaged more than 18 gm. per day.

At the time of admission there was evidence of widespread vascular disease, manifested by retinal, cardiac, and renal disease and by hypertension. If the patient received only a single daily dose of any type of long-acting insulin, no dietary program could be found that would eliminate extreme fluctuations of blood sugar. On a quantitative formula diet administered hourly throughout the 24 hours through a nasogastric tube, adequate diabetic control was obtained only by the administration of insulin at six-hour intervals.

The patient was given large amounts of anabolic steroids in an effort to decrease protein catabolism, and hence to diminish the work of the kidney. At intervals he received steroids, which from animal evaluation appeared to have significant pituitary inhibitory activity. Despite such measures, his course was steadily downhill, as manifested chemically by a rising blood urea nitrogen and serum inorganic phosphorus. The patient expired on June 10, 1953. The fundamental cause of death was renal insufficiency.

G.A.R., a 27-year-old Mexican girl, had the onset of diabetes at the age of 12. Her first admission to Highland-Alameda County Hospital occurred in 1940. At the first admission to the metabolic ward, in November 1952, her major complaint was progressive loss of vision involving both eyes.

The average daily output of urinary protein exceeded 7 gm., but the urinary sediment was essentially normal, and the phenolsulphonephthalein excretion test was within the normal range. The plasma total cholesterol on an average "diabetic diet" exceeded 500 mg. per 100 cc. and plasma phospholipids were proportionately increased. There was no hypertension, azotemia, or gross cardiac abnormality.

As in the case of patient D.I.D., noted above, good diabetic control could be obtained only by the combination of a quantitatively constant formula diet, administered hourly throughout the 24 hours, in association with insulin at six-hour intervals. Some of these findings are shown in figure 2.

Over a period of twelve months, there was a measurable decrease in renal efficiency, together with some progressive elevation in blood pressure. It was obvious that with any or all of the usual therapeutic measures, this

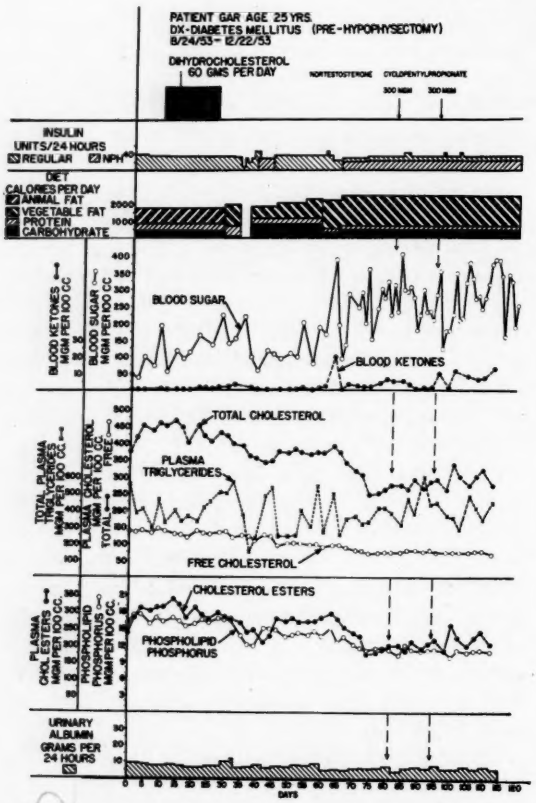

FIG. 2. Good diabetic control could be achieved in patient G.A.R. only by a combination of hourly feeding and six-hourly insulin. The fall in plasma cholesterol was associated with a high vegetable fat intake.

patient would follow the same course as patient D.I.D. and other similar patients who had been studied in the clinics and general wards over the past several years. The decision to carry out hypophysectomy was therefore made, and she was one of the four cases in which this procedure has been employed.

CLINICAL AND BIOCHEMICAL EVALUATION OF HYPOPHYSECTOMY IN FOUR CASES

In view of the hazardous nature of the procedure, and of the lack of available information regarding optimal postoperative management of such patients, it was felt that initially surgery should be carried out only in individuals in whom all clinicians were agreed that a fatal outcome was inevitable on the basis of any conventional therapy. The first two patients, therefore, represent individuals who, because of extensive renal insufficiency, manifested by azotemia on a low protein intake, were poor operative and postoperative risks.

Case 1. K.I.N., a 31-year-old woman, had the onset of her diabetes at the age of 13. Diabetic management had always been poor. Clinical vascular disease was first manifested in the form of visual impairment. For more than twelve months before admission to the hospital the patient had been in or on the verge of heart failure. The average urinary albumin excretion per day exceeded 15 gm. The blood urea nitrogen was significantly elevated on a protein intake of 40 gm. per day. The average insulin requirement on a 1500-calorie diet was more than 60 units.

Hypophysectomy was carried out on December 2, 1953. Immediate and later postoperative management will be discussed below. The patient was permitted to leave the hospital on March 22, 1954, although with misgivings on our part in view of her lack of anything approaching co-operation as regards diet during hospitalization. She returned to the hospital on April 5 and died on April 16 as the result, fundamentally, of renal and cardiac insufficiency.

Case 2. S.E.S., a 26-year-old man, had the onset of his diabetes at the age of 13. Diabetic management had been relatively poor. Clinical vascular disease first became obvious in August 1951 in the form of progressive eye involvement. At the time of admission to the hospital extensive vascular disease was manifested by grossly abnormal cardiac and renal function, extensive retinal disease and hypertension. Hypophysectomy was carried out on December 14, 1953.

The patient was permitted to go home on March 7, 1954. He left the hospital completely free of edema, very mildly azotemic, and apparently in remarkably good condition considering the extent of his vascular disease. He returned to the hospital on March 19. During his time at home he had used excessive amounts of salt, with the prompt appearance and progression of edema. On admission he was found to have pleural and pericardial effusion. He died on March 26, the primary cause of death being coronary occlusion.

The problems encountered in Cases 3 and 4 were of significantly lesser magnitude than in the first two, because each patient possessed a reasonable amount of viable kidney tissue.

Case 3. The third hypophysectomy (January 11, 1954) was performed in patient G.A.R. Surgery and early convalescence were uneventful. On the tenth day the patient contracted a gastrointestinal infection which was epidemic at the time. A urinary tract infection was superimposed

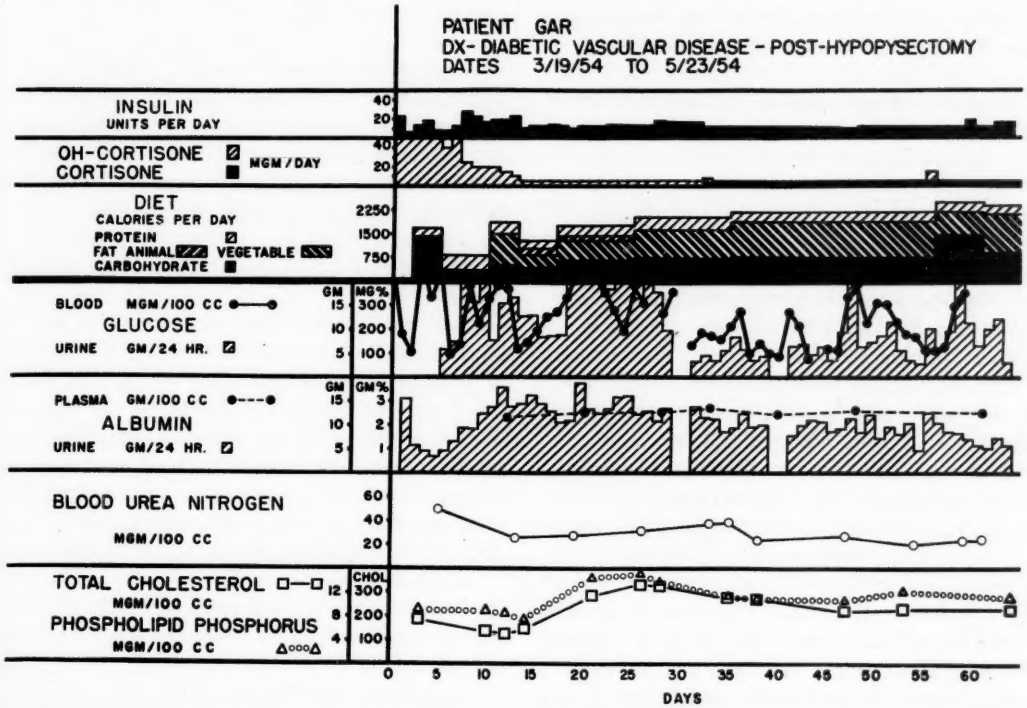

FIG. 3. Medication, diet, and some laboratory findings in patient G.A.R., during the second two-month postoperative period. Six weeks later, blood sugar values were constantly within the normal range on a dosage of ten units of NPH insulin and 15 mg. of cortisone acetate daily. By July 20, 1954, twenty-four-hour urinary excretion of albumin approached 3 gm. per day, visual improvement was unequivocal, and erythropoesis approached normal for the first time during the two-year period of observation.

upon this, and for a period of more than a month her condition was precarious. At the present time she is doing well and is able to be increasingly active. Urinary albumin appears to have decreased slightly. Some of her data are shown in figure 3.

At the time of submission of this paper (July 20, 1954), the patient showed a very significant decrease in albuminuria (average less than 3.5 gm. per day), improvement in vision, and, for the first time during her two-year period of observation, evidence of normal erythropoiesis.

Case 4. L.A.C., a 30-year-old man, whose diabetes manifested itself at the age of 16, was admitted because of progressive blindness. He had moderate albuminuria, some hypertension, no azotemia, and no clinical cardiac damage. Hypophysectomy was performed on March 9, 1954. Major hemorrhage was encountered during curettement of the sella. Convalescence was uneventful.

Hypertension has disappeared, but the cortisone requirement and relatively slight (30 per cent) decrease in insulin requirement appears to indicate beyond much question a considerably less than total hypophysectomy. In view of the gradual progression of pituitary insufficiency in some patients with Sheehan's syndrome, the patient will be observed for some time before further surgery is considered.

PREOPERATIVE AND POSTOPERATIVE MANAGEMENT

The preoperative and postoperative management in these patients, in terms of principles and practice, is as follows.

In planning the preoperative preparation of a patient for hypophysectomy, and the postoperative management, one needs to enumerate the specific problems that such patients present, entirely apart from hypophysectomy in itself. Fundamentally these problems are those associated with diabetes, added to those resulting from vascular damage, including most prominently myocardial damage and renal insufficiency. Anemia and hypoproteinemia may also be major problems.

Following hypophysectomy, one adds to the preceding all those factors attendant upon pituitary insufficiency in such a patient. These include hypoadrenocorticism, hypothyroidism, and hypogonadism, as well as a more or less rapid transition from a state of insulin resistance to insulin hypersensitivity.

Preoperative Preparation

Diet. For two days prior to surgery, the patient is maintained *only* on an infusion containing glucose, sodium chloride, potassium chloride, insulin, and B complex vitamins. Specifically we have administered 5 per cent glucose in water, at a rate of 150 cc. per hour, each liter containing 2 gm. of potassium chloride, 10 to 20 units of insulin, and sodium chloride as indicated in each individual. We have felt it well to err on the low rather than the high side insofar as sodium is concerned, to avoid the likelihood of postoperative cerebral edema.

Blood. Transfusions are given as needed to maintain a hemoglobin of 12 gm. or more per 100 cc.

Hormonal Medication. Fifty milligrams of cortisone acetate is administered by intramuscular injection every 12 hours during the two-day period prior to operation. When the patient goes to surgery, 100 mg. of hydrocortisone is added to the infusion noted below. This is administered at a rate of 100 cc. per hour.

Testosterone propionate, 50 mg. daily, is administered, beginning at least three days before surgery. This has a mild sodium-retaining effect and a major protein anabolic effect. The latter diminishes the load on the kidney in terms of disposition of the products of protein catabolism.

Antibiotic Therapy. Beginning twelve hours before the patient goes to surgery, 250 mg. of terramycin or 200 mg. of achromycin is added to each liter of intravenous solution. The reasons for this are (1) the generally poor resistance of these patients to infection, and (2) the increased possibility, at least theoretically, of dissemination of infection during the period of intensive adrenocortical steroid therapy.

Operative Management

At the time the patient goes to surgery, the standard infusion solution is made up as follows. To each liter of 5 per cent glucose in distilled water is added 2 gm. of potassium chloride, 2 gm. of sodium chloride, 250 mg. of terramycin, and 2 units of insulin. As noted above, the first liter contains 100 mg. of hydrocortisone. Additional intravenous hydrocortisone is used only if indicated by significant decrease in pressure, or other manifestations of shock.

Supplemental Insulin Administration. A Foley catheter is placed in the bladder before the patient goes to the operating room. Throughout operation, urinary volume is recorded on an hourly basis and semiquantitative tests for urinary sugars are recorded on a 30-minute basis. Insulin is given at 30-minute intervals through the intravenous tubing as indicated, on the basis of 5, 10, 15 or 20 units for 1 to 4 plus tests respectively before hypophysectomy, and 2, 4, 6 or 8 units after hypophysectomy.

Anesthesia is administered as indicated in individual cases. This will be reported later by Dr. Bruce Anderson.

Surgery. The transfrontal approach, such as that used for a pituitary tumor, was chosen for several reasons. It is one with which the average neurosurgeon is best acquainted; it seems safest for the protection of optic nerves, under direct vision, and for the control of any local hemorrhage that might occur; and with this approach one works in a surgically clean field.

A choice of scalp incisions can be used. The hairline incision, which will leave no visible scar, may be the incision of choice, but in these two cases a horseshoe-shaped unilateral frontal incision was made so that the hinge of the scalp flap would be over the brow. A relatively small frontal flap was turned down, care being taken to avoid entering the frontal sinus. The dura was stripped from the roof of the orbit for a distance of 2.5 cm. from the anterior extent of the orbital roof. The dura covering the undersurface of the frontal lobe furnishes protection from the trauma of retractors.

As dissection is carried posteriorly, the ipsilateral olfactory nerve is easily identified and cut. Cutting this nerve avoids avulsion of the fibers of the olfactory nerve from the cribiform plate and also permits better exposure of the sella turcica. After the anterior clinoid process and the optic nerve are identified, dissection is carried posteriorly until the optic chiasm can be seen. The arachnoid can then be ruptured. Elevation of the undersurface of the brain results in displacement of the chiasm, since the chiasm is adherent to this surface and will retract with cortical tissue. This avoids the danger associated with direct pressure on the chiasm.

The approach to the hypophysis is made in the interval between the tuberculum sella, the optic chiasm, and the optic nerves. The opening in the diaphragm is easily identified by a protrusion of the pituitary gland plus the hypophyseal stalk. In only one case was the stalk large enough to require clipping with a silver clip. The aperture in the diaphragm is dilated with blunt-nosed

rongeurs, and the pituitary gland is removed piecemeal with a blunt pituitary rongeur, tiny malleable silver curettes, and by suction. When as much of the gland as possible is removed, the remainder is coagulated using Zenker's solution on small cotton pledgets.

The wound is closed by suturing the incision in the dura, replacing the bone flap and securing it with several very fine stainless steel wires, and suturing the scalp in the usual fashion.

Bleeding was very bothersome on occasion. Profuse bleeding occurs from the incisions and tears in the diaphragm and sellae. More serious hemorrhage occurs from the hypophyseal capsule. This can be controlled by packing the sella turcica with oxycel cotton if necessary. In one case, gelfoam was used and left in the sella turcica. In this case a very disturbing amount of spinal fluid collected under the scalp flap and persisted for several weeks in spite of repeated aspirations. It disappeared rapidly following the local instillation of free-hydrocortisone suspension into the pocket.

Postoperative Management

Following surgery, one is faced with the problem of maintaining a proper balance between corticosteroids and insulin, from the standpoint of carbohydrate metabolism; and corticosteroids, electrolytes, albumin and fluids, from the standpoint of a damaged cardiovascular-renal system. Obviously, the greater the amount of cardiorenal insufficiency, the greater the problem.

Infusions. An infusion, identical with that used during surgery, is continued during the first several days following surgery. Modifications are made only as specifically indicated by frequent serum electrolyte determinations, as well as by the clinical status of the patient. Hourly recordings of urine volume are made, and the rate of infusion is adjusted on this basis. During the first four postoperative days, we have maintained the patient in a mildly negative fluid balance to lessen the likelihood of cerebral edema.

Albumin and Blood. Serum albumin is administered in amounts sufficient to replace the urinary loss. Blood is administered as indicated.

Hormonal Medication. During the first three days following surgery, cortisone acetate is administered intramuscularly at the rate of 50 gm. every 12 hours. Thereafter the dose is progressively decreased, as indicated by urinary output, blood pressure, and blood sugar. By the tenth postoperative day, the patient will probably not require more than 5 mg. of hydrocortisone four times daily, or 6.25 mg. of cortisone acetate four times daily by mouth.

One hundred milligrams of testosterone cyclopentylpropionate is administered the day before surgery and weekly thereafter to minimize protein catabolism.

Insulin Administration. The urine is tested with Benedict's solution every hour during the first four days following surgery. Regular insulin is administered through the intravenous tube at hourly intervals on the basis of 0 for blue, 2 units for green, 4 units for yellow, 6 units for orange, and 8 units for red. As soon as the patient is maintained on an adequate diet, regular insulin is administered three or four times daily "by test," continuing for a period of several days, and is then replaced by a single dose of long-acting insulin. If removal of the pituitary tissue has been adequate, it is probable that the insulin dose will be less than 20 per cent of the preoperative requirement.

Diet. As soon as the patient is able to take food by mouth, he is given small amounts of soft and liquid foods every two hours. By the tenth day he should be able to resume a mixed diet adequate for his size and weight. In those patients with renal insufficiency, the protein intake should not exceed the amount required to compensate for endogenous protein catabolism, plus loss of urinary albumin. Because of the insulin hypersensitivity, six or seven small meals evenly distributed throughout the day are essential. Vitamin supplements should be used generously.

Electrolytes. The long-term and short-term problem in regard to electrolyte regulation appears to be directly proportional to the degree of renal damage. On the one hand, one has a tendency to renal acidosis with resultant loss of fixed base; on the other, a tendency to abnormal retention and distribution of sodium, that is, intracellular replacement of potassium by sodium. The latter factor, plus the hypoproteinemia attendant upon proteinuria, make edema in general and cerebral edema in particular a major problem. Luft and Olivecrona,[3] who as far as we know are the only other group who have performed hypophysectomy in diabetics, had a high mortality rate from cerebral edema, presumably as the result of these factors. From our own experience, it appears that cerebral edema may be avoided or controlled by the judicious use of albumin (figure 4); the administration of sufficient sodium and potassium to maintain a plasma level of the former slightly below normal and of the latter slightly above normal; the total avoidance of desoxycorticosterone, and the avoidance of either overdosage or underdosage with cortisone. Mercurial diuretics and ammonium chloride may also be required. From the

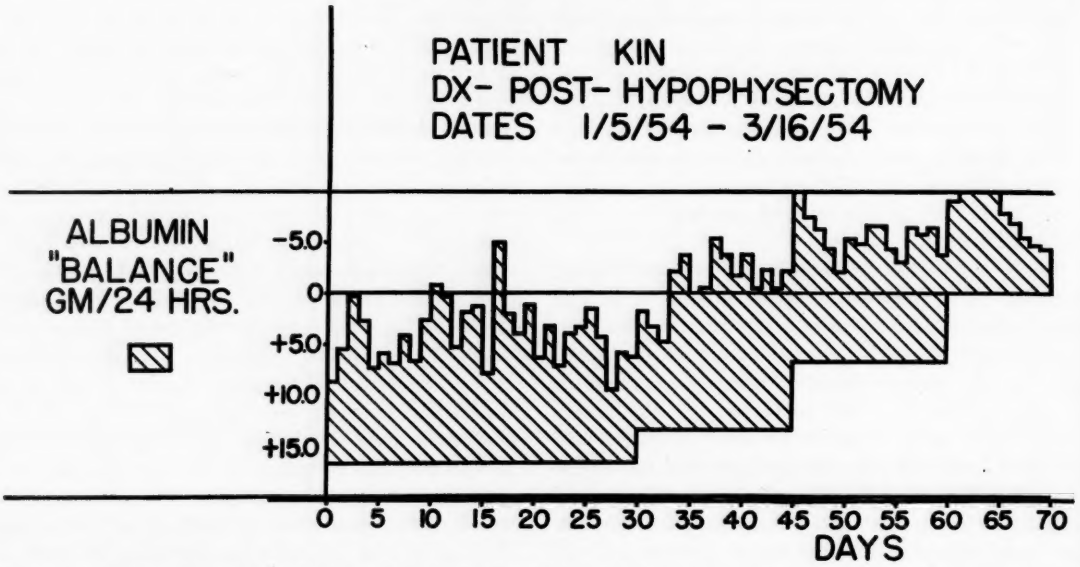

FIG. 4. In the first few weeks after hypophysectomy, the infusion of large amounts of albumin may be necessary to maintain a positive balance and thus to prevent cerebral edema.

foregoing, it is obvious that constant and dependable laboratory control is essential.

TENTATIVE CONCLUSIONS (AS OF JUNE, 1954)

Conclusions as to the value of hypophysectomy in patients with malignant diabetic vascular disease will not be possible until the lapse of much more time. Our impressions as of this date are as follows:

1. Hypophysectomy in these patients will change an insulin-resistant diabetes to an insulin-hypersensitive diabetes.

2. Undue insulin hypersensitivity can be balanced by the judicious use of cortisone or hydrocortisone. The dose of adrenal steroids should be kept at a minimal level compatible with well-being and diabetic control. Desoxycorticosterone should be avoided.

3. Hypophysectomy should not be carried out in patients with negligible renal reserve. For the present, we have arbitrarily decided that no patient shall be considered for surgery unless he is able to maintain a normal blood urea nitrogen on a diet which contains 50 gm. of protein and is nutritionally adequate in all other respects. This is obviously a rule of thumb and subject to later revision and refinement.

4. At the other extreme, no diabetic patient should be selected for hypophysectomy unless he has evidence of progressive retinal and/or renal damage, in association with diabetes which cannot be well controlled by proper diet and insulin. One should view with alarm, as a candidate for hypophysectomy, any patient who has been a notoriously unco-operative diabetic. The superimposition of panhypopituitarism upon diabetes and diabetic vascular disease calls for a reasonable modicum of intelligence and emotional stability on the part of the patient, if one is to have any reasonable chance for a long-term good result.

5. In addition to a well selected patient, if hypophysectomy is to be considered, the following probably represent the minimal requirements: a. A medical-surgical team familiar with the management of complex endocrine-metabolic disease and with difficult neurosurgery. b. Excellent special nurses during the first five or more days following surgery. c. Excellent anesthesia. d. A first-class laboratory capable of keeping one constantly abreast of developments in regard to serum electrolytes and other required biochemical determinations.

FURTHER PROGRAM

We plan to observe our present hypophysectomized patients for a period of perhaps another three months. If by that time the clinical and metabolic findings continue to be encouraging, approximately one hypophysectomy per month will be performed thereafter.

Also under consideration is the matter of adrenal-

ectomy in alternate patients for a certain period, to determine whether the net effect upon the diabetic state (and eventually upon the vascular disease) will be significantly different in the two procedures. Despite the experimental findings in regard to the diabetogenic effects of pituitary preparations allegedly free of corticotropin, it is still to be established whether pituitary factors other than ACTH play a major role in the pathogenesis and progression of clinical diabetes. From a technical standpoint, as well as from the standpoint of long-term management, adrenalectomy is to be preferred to hypophysectomy.

At the same time that the above procedures are under way, we are constantly evaluating steroid preparations which, on the basis of animal evaluation, have been shown to have pituitary inhibitory effects. It has been observed independently by Edgar Gordon[4] and our group[5] that cortisone, at least in some individuals, may have in a sense a paradoxical effect; that is, there may be a stabilizing effect upon blood sugar, and even on occasion a decrease rather than an increase in insulin requirement. In patients with significant renal damage, cortisone is specifically and emphatically contraindicated because of the increased protein catabolism and increased amount of work load for the kidney.

Animal experimental data in regard to beta-hydroxyprogesterone suggest the possibility of pituitary inhibition.[6] Early observations with this material in human subjects in our laboratory may be compatible with such observations. The material, however, has a definite corticoid effect, and hence, at least for the present, must be considered to be contraindicated in the presence of renal damage of significant degree.

Testosterone and estrogen appear to inhibit the production and/or the effects of pituitary growth hormone to some degree. In our hands, they have not produced a consistent modification in the severity of diabetes in insulin-resistant diabetics, with the exception of two individuals in whom thyrotoxicosis coexisted with the diabetes.

It seems to us sufficiently probable that potent pituitary-inhibiting compounds will be available within the next few years to make it mandatory that *hypophysectomy should be considered only in those individuals in whom the progression of vascular disease is too rapid to justify procrastination.*

Finally, we should again like to emphasize that we belong to that school of thought which is firmly convinced that optimal diabetic control will delay significantly the progress of vascular disease, and hence that a relaxed approach to diabetic management, from the standpoint of the best possible regulation of diet, insulin, and activity, is a thoroughly unwarranted procedure.

SUMMARY

Early experience with hypophysectomy in 4 cases of diabetes with malignant progressive vascular disease is presented. One patient died of renal and cardiac insufficiency nearly five months after operation and another died of coronary occlusion three months after operation. Two patients are living five and three months after operation respectively.

DISCUSSION

FRANCIS D. W. LUKENS, M.D., (*Philadelphia*): There is nothing more stimulating than to hear a well planned effort to help a basically incurable situation. Dr. Kinsell has made a wise beginning from which certain changes may perhaps be made. He brought up the queston frequently asked in this Association: What is the control of diabetes? Since none of us knows what that is, I will only call your attention to the fact that his good outline of the possible causes of vascular disease raised just this question. To reword it, what must we control to prevent these vascular lesions since the nondiabetic does not develop them at the same rate?

He selected for his attempt to help these people who are otherwise incurable, patients with advanced renal damage. I think he did the right thing under the circumstances, but having reported to you that at least two of these people died from renal insufficiency, I believe that he will select a different type of patient in the future. I have no right to predict what you will do, Dr. Kinsell, but this is just my reaction because we had a similar experience in the study of adrenalectomy for severe hypertension. In this work, patients with renal insufficiency died in three to four months. It is important to learn that hypophysectomy likewise fails to halt advanced renal disease. Now that we know this, it would seem logical to select for future surgical treatment the diabetic patients who are blind, but who have good renal function, at least in terms of the blood urea nitrogen.

There is a distinct possibility that all patients with vascular disease may not react in the same way to hypophysectomy, and I should anticipate this possible event on the basis of our experience with adrenalectomy for hypertension in which about 20 to 30 per cent of the patients have had rather striking results, and the remainder very modest results, indeed.

Finally, I hope that Dr. Kinsell can give us more

information about the effect upon the vascular lesions for which hypophysectomy was done. This will be done by following the appearance of the retina, and we can look forward with considerable hope on the basis of Poulsen's now famous report and of the experience with hypertensive retinopathy which is not the same thing, but which has responded remarkably well in many instances.

On the basis of the observations so far available, it is concluded that major renal insufficiency is a contraindication to such surgery; that for the present, at least, patients with early and slowly progressing vascular disease should not be considered for surgery; and that in those diabetics with progressive vascular damage who fall between these two extremes, hypophysectomy should be carried out only under optimal conditions from the standpoint of medical, surgical, and nursing care and laboratory control.

A considerable time must elapse before we shall be able to evaluate properly the place of hypophysectomy in the management of such cases.

ACKNOWLEDGMENTS

The wholehearted co-operation of Drs. Alfred F. Anderegg, Robert J. Alderson, George Murphy, and David E. Starrett (Residents in Medicine), and of many members of the nursing staff of the two hospitals, particularly Marjorie Coelho and Faye T. Land, contributed in a major degree to the postoperative progress of these patients.

Grateful acknowledgment is made to Merck & Company for supplies of cortisone and hydrocortisone; to The Upjohn Company for supplies of β-hydroxyprogesterone, testosterone cyclopentylpropionate, and nortestosterone cyclopentylpropionate; and to Schering Corporation for supplies of ethinyl estradiol and testosterone propionate.

Grateful acknowledgment is made to Miss Lucy Ward Stebbins for financial support of a portion of this work.

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The Prospects of Longevity

The statisticians of the Metropolitan Life Insurance Company are trained and accustomed to trip lightly through maze-like sets of figures over which others merely trip. Important, pleasant to study and not too complicated are those relating to the increasing length of life in the United States.

Based on the experience in 1951 the average duration of man's corporeal grip has increased to a new high of sixty-eight and five-tenths years—a gain of approximately twenty years since the beginning of the dynamic twentieth century. Obviously, the improved expectation has been greatest in the younger ages, since the infant mortality affects so greatly the over-all picture of life expectancy; in 1900, 1 in 8 newborn infants failed to live out its first year, whereas only 1 in 8 of those born in 1951 will fail to achieve its fiftieth birthday.

Bearing some remote resemblance to the half lives of isotopes, any person at any age has some sort of life expectancy; the younger he may be the better are his chances for living a considerable number of years, although, paradoxically enough, the enfeebled dotard of ninety-nine has an infinitely better chance of reaching the century mark than has the most robust one-year-old.

To return to more precise figures, eleven years have been added to the average life expectancy at age five, nine years at age twenty, and five years at age forty. Even at age sixty-five two and three-tenths years have been added to the former expectation, with the result that the average man of sixty-five can expect thirteen additional years, and the average woman fifteen and a half. Once the perils of infancy are passed seventy-one years is the average term of life, and for those who have passed fifty, three quarters of a century is a reasonable expectation—bar hell and high water.

From "Great Expectations," an editorial in the *New England Journal of Medicine*, Sept. 30, 1954.

Adrenalectomy in Human Diabetes

Effects in Diabetics with Advanced Vascular Disease

James T. Wortham, M.D., and James W. Headstream, M.D., Little Rock, Arkansas

In 1949, Green, Nelson, and Dodds[1] reported favorable results from adrenalectomy upon the vascular disease of a patient who had a malignant hypertensive syndrome in association with severe diabetes. The adrenalectomy was not total, but was sufficient to cause severe adrenal insufficiency. Low-dosage adrenal replacement therapy was given successfully, despite the fact that this occurred prior to the advent of modern, practical adrenal replacement therapy. Early in 1953 Poulsen[2] reported marked improvement in the retinopathy of a young diabetic woman after the development of hypopituitarism due to postpartum pituitary necrosis (Sheehan's syndrome). The hypopituitarism in this patient was marked initially by severe hypoadrenal symptoms. With these encouraging stimuli, and in consideration of the poor results of treatment of degenerative vascular disease in diabetics by other methods, it was decided to attempt the palliation of arteriolar degenerative lesions in a series of diabetics by bilateral, total adrenalectomy. The advent of simple adrenal replacement therapy contributed much to making the attempt practical and relatively safe. We first reported the initial results in the first series of seven patients in December 1953.[3] At that time, several of the patients had been followed for only a very short period. We present here data on the same series of patients.

CLINICAL MATERIAL

Case 1. The patient, L. C., is a 23-year-old married woman. Her diabetes had been very "brittle" and labile during most of its 13 years' duration, and she has experienced diabetic coma seven times. Four years before admission to our service she had experienced severe hypertension and proteinuria during a pregnancy. For over three years hypertension, chronic edema, and poor diabetic control had been constantly symptomatic. Progressive and rapid visual loss had been noted for one year.

The preoperative blood pressure averaged 160/120. Fourteen months after adrenalectomy it averages 107/80. The average preoperative value for serum nonprotein nitrogen was 55 mg. per 100 cc. and now averages 48 mg. Urinary protein has fallen from an average of 5.5 gm. per 24 hours to 0.75 gm. Close diabetic control was impossible preoperatively, but crude control was obtained with 70 units of insulin daily. Under present control the patient is held to normoglycemia with 20 units of insulin daily. These changes are depicted graphically in figure 1. Chronic generalized edema has disappeared, and there has been remarkable improvement in visual acuity. Changes in one optic fundus during the first four months after adrenalectomy are shown in figure 2; there has been little change during the 10 months since then. The patient has regained a convincing sense of well-being.

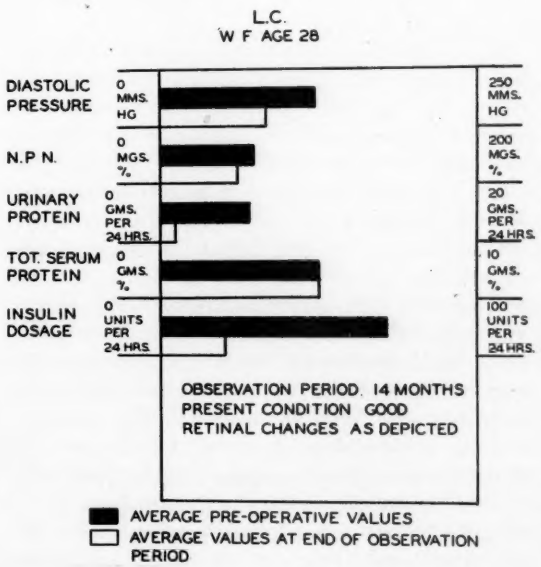

FIGURE 1

From the Department of Medicine and the Division of Urology, Department of Surgery, University of Arkansas School of Medicine, Little Rock, Ark. Research paper 1003, Journal Series, University of Arkansas.

Read with modifications at the 14th Annual Meeting of the American Diabetes Association in San Francisco on June 20, 1954.

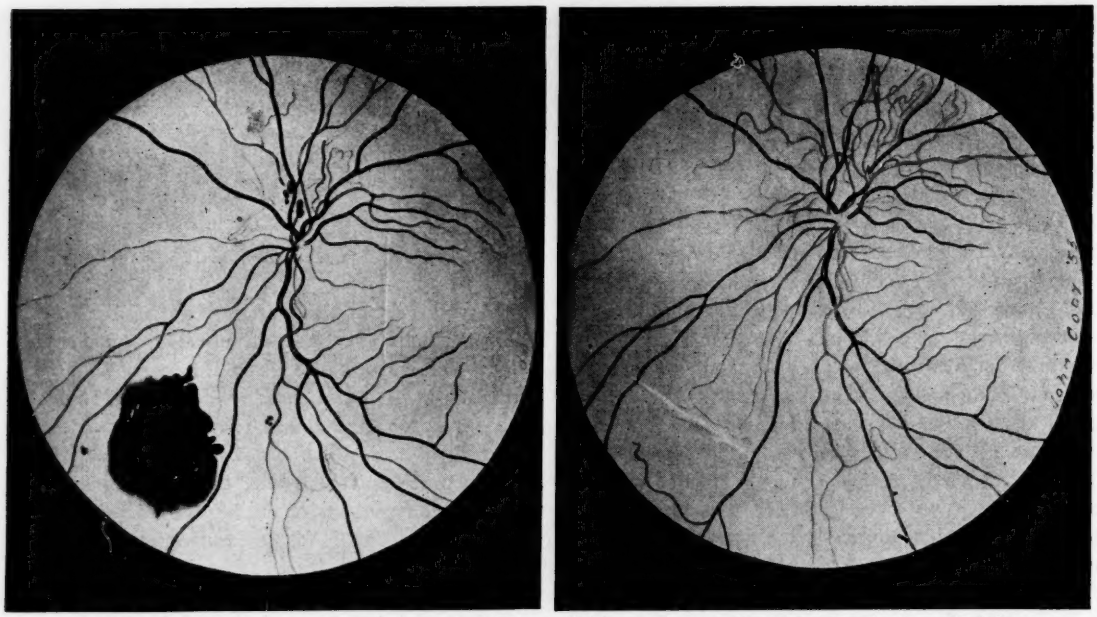

FIG. 2. Optic fundus of a patient before adrenalectomy (left) and four months after adrenalectomy (right).

Case 2. This patient, G. H., is a 54-year-old man. Diabetes had been diagnosed 22 years before admission, but after a few months of diet therapy, glycosuria had disappeared. From that time until admission, no diabetic precautions or observations had been taken. The presenting complaints were severe, intractable headaches and rapid loss of vision.

The average preoperative blood pressure was 180/93. Thirteen months after surgery the blood pressure averages 165/85. The average preoperative serum nonprotein nitrogen was 55 mg. per 100 cc. During a routine hospital observation after adrenalectomy it rose sharply. This proved to be the first evidence of adrenal insufficiency, due to inadequate replacement therapy. Since correction, there has been a progressive decrease in nitrogen retention, and the average nonprotein nitrogen is now 74 mg. (figure 3). The urinary protein has fallen from a preoperative average of 6.5 gm. per 24 hours to 4 gm. The patient had never had stable control with insulin preoperatively, and diet control was not satisfactory. Insulin was used during the acute, operative period of stress, and now the blood sugar control is adequate with diet therapy alone. There has been no further progression in his severe diabetic retinopathy. Retinal hemorrhages have ceased, retinal edema has decreased, and the visual acuity is moderately improved. The patient has a sense of well-being, and almost all symptoms have disappeared.

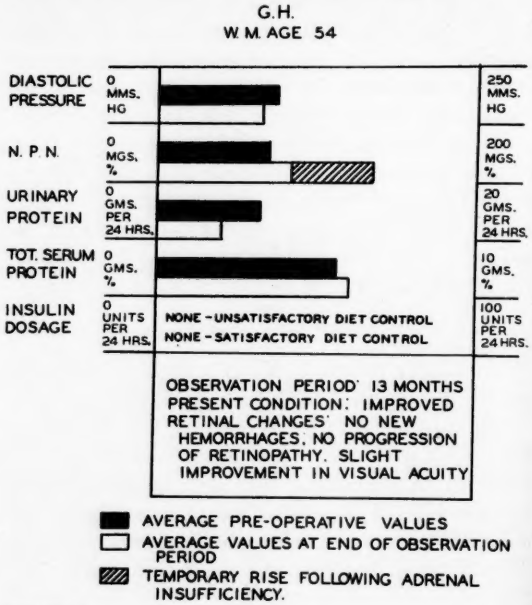
G.H.
W.M. AGE 54
DIASTOLIC PRESSURE
0 MMS. HG
250 MMS. HG
N. P. N.
0 MGS. %
200 MGS. %
URINARY PROTEIN
0 GMS. PER 24 HRS.
20 GMS. PER 24 HRS.
TOT. SERUM PROTEIN
0 GMS. %
10 GMS. %
INSULIN DOSAGE
0 UNITS PER 24 HRS.
100 UNITS PER 24 HRS.
NONE - UNSATISFACTORY DIET CONTROL
NONE - SATISFACTORY DIET CONTROL
OBSERVATION PERIOD 13 MONTHS
PRESENT CONDITION: IMPROVED
RETINAL CHANGES: NO NEW HEMORRHAGES, NO PROGRESSION OF RETINOPATHY. SLIGHT IMPROVEMENT IN VISUAL ACUITY
AVERAGE PRE-OPERATIVE VALUES
AVERAGE VALUES AT END OF OBSERVATION PERIOD
TEMPORARY RISE FOLLOWING ADRENAL INSUFFICIENCY.

FIGURE 3

Case 3. This patient, B. R., was a 40-year-old married woman. Her entire eight years of diabetes had been hectic, and she had never been closely regulated. Several

episodes of diabetic coma and innumerable severe insulin reactions had been experienced. On admission she was in a state of hypertensive encephalopathy complicated by mild diabetic acidosis.

The average preoperative blood pressure was 200/100. Four and one-half months after surgery, before death, it averaged 190/115. The serum nonprotein nitrogen rose progressively from a preoperative average of 65 mg. per 100 cc. to an average before death of 120 mg. Only a slight decrease in urinary protein occurred, and there was no rise in the subnormal total serum proteins (figure 4). The insulin requirement fell from 40 to 30 units daily, and the degree of diabetic control was much improved. Despite largely unfavorable results, there was visual improvement, based on cessation of retinal hemorrhages and resorption of retinal edema. Generalized edema had been intractable before adrenalectomy but became readily controllable after it. Death occurred from a cerebral vascular accident during a course marked by progressive renal failure.

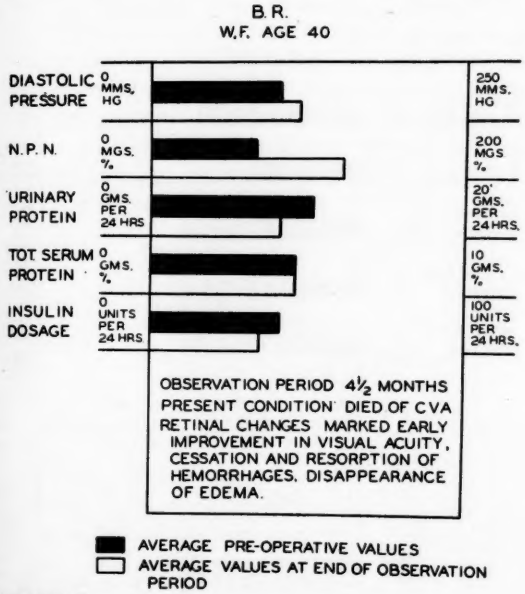
B. R.
W. F. AGE 40
DIASTOLIC PRESSURE
0 MMS. HG
250 MMS. HG
N. P. N.
0 MGS. %
200 MGS %
URINARY PROTEIN
0 GMS. PER 24 HRS
20 GMS. PER 24 HRS.
TOT SERUM PROTEIN
0 GMS. %
10 GMS. %
INSULIN DOSAGE
0 UNITS PER 24 HRS
100 UNITS PER 24 HRS.
OBSERVATION PERIOD 4½ MONTHS
PRESENT CONDITION DIED OF CVA
RETINAL CHANGES MARKED EARLY IMPROVEMENT IN VISUAL ACUITY, CESSATION AND RESORPTION OF HEMORRHAGES. DISAPPEARANCE OF EDEMA.
AVERAGE PRE-OPERATIVE VALUES
AVERAGE VALUES AT END OF OBSERVATION PERIOD

FIGURE 4

Case 4. The patient, M. T., was a 21-year-old nulliparous married woman. Five episodes of diabetic coma, innumerable severe insulin reactions, and gross neglect had characterized her 14 years of diabetes. Fifteen months before admission to the University service, both optic globes had been removed due to intractable pain from secondary glaucoma. Irremediable edema had been present for one year, and the patient was admitted in a state of hypertensive encephalopathy.

The average preoperative blood pressure was 220/140. Eight months after adrenalectomy, at the last observation before death, it was 210/140. The average serum nonprotein nitrogen fell from 51 mg. per 100 cc. before surgery to 45 mg. The urinary protein fell from a preoperative average of 5.2 gm. per 24 hours to 2.7 gm. before death. The insulin requirement fell from 60 units daily before surgery to 35 units daily before death (figure 5). The patient became edema-free and encephalopathic symptoms disappeared. There was an improvement in well-being. She remained active and asymptomatic, with her diabetes under good control, until shortly before death. She died of adrenal insufficency after leaving the care of the University service.

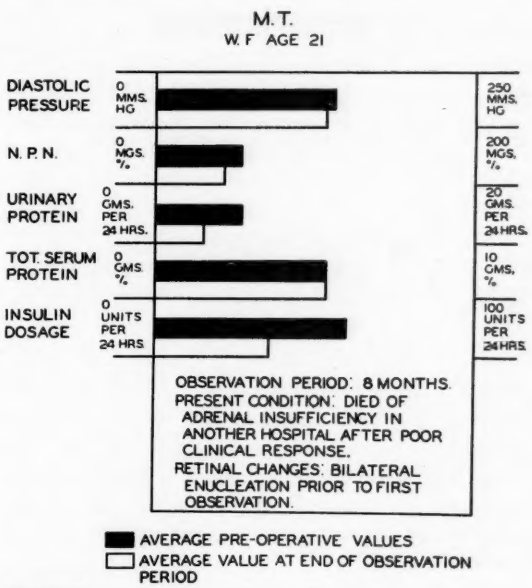
M. T.
W. F AGE 21
DIASTOLIC PRESSURE
0 MMS. HG
250 MMS. HG
N. P. N.
0 MGS. %
200 MGS. %
URINARY PROTEIN
0 GMS. PER 24 HRS.
20 GMS. PER 24 HRS.
TOT. SERUM PROTEIN
0 GMS. %
10 GMS. %
INSULIN DOSAGE
0 UNITS PER 24 HRS.
100 UNITS PER 24 HRS.
OBSERVATION PERIOD: 8 MONTHS.
PRESENT CONDITION: DIED OF ADRENAL INSUFFICIENCY IN ANOTHER HOSPITAL AFTER POOR CLINICAL RESPONSE.
RETINAL CHANGES: BILATERAL ENUCLEATION PRIOR TO FIRST OBSERVATION.
AVERAGE PRE-OPERATIVE VALUES
AVERAGE VALUE AT END OF OBSERVATION PERIOD

FIGURE 5

Case 5. The patient, E. W., is a 27-year-old man. After several years of good diabetic control, his adolescent and adult years were characterized by very poor control. The total duration of his diabetes was 18 years. Onset of rapid visual loss occurred two years before admission. Bilateral severe retinal detachment and retinitis proliferans were present on admission.

The average preoperative blood pressure was 166/108. Ten months after adrenalectomy it averages 150/102. The average preoperative serum nonprotein nitrogen was 42.8 mg. per 100 cc., and it now averages 56.5 mg. Urinary

protein has risen from an average preoperative value of 6.56 gm. per 24 hours to a present average of 8.31 gm. Initial diabetic control was achieved with an average of 67 units of insulin daily. The diabetes is now well controlled with 45 units of insulin daily (figure 6). There has been no change in the retinopathy.

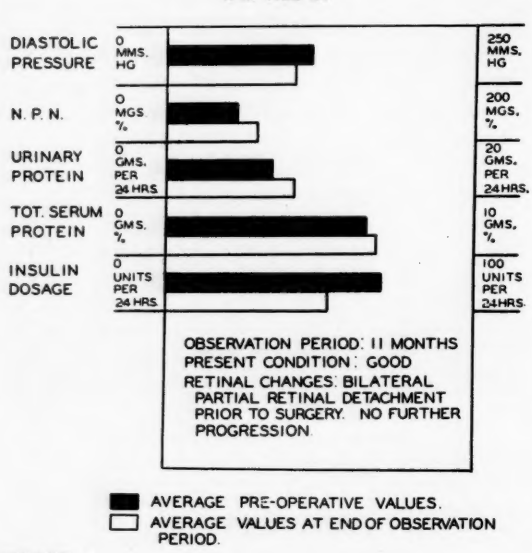

FIGURE 6

Case 6. The patient, M. G., is a 56-year-old married woman. Diabetic symptoms had been present for several years but had been diagnosed only three years before admission. Chronic edema, severe headaches, and rapid visual loss had been noted for one year. Retinal examination revealed advanced arteriolosclerosis, innumerable small retinal hemorrhages, retinal edema, and moderate exudation.

The average preoperative blood pressure was 160/95. Ten months after adrenalectomy it averages 107/73. The average preoperative serum nonprotein nitrogen was 39.5 mg. per 100 cc., and it now averages 34 mg. Before operation the urinary protein averaged 0.71 gm. per 24 hours; after operation it fell below measurable quantities. Good diabetic control was established with 20 units of insulin daily before surgery. No insulin is now required for close control. There has been cessation of retinal hemorrhages and clearance of retinal edema, with significant improvement in visual acuity (see figure 7).

Case 7. The patient, R. T., was a 29-year-old man. Diabetes had been present for 24 years and he had

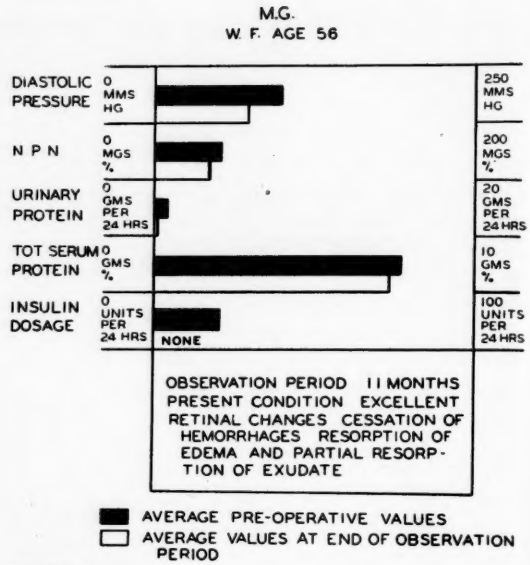

FIGURE 7

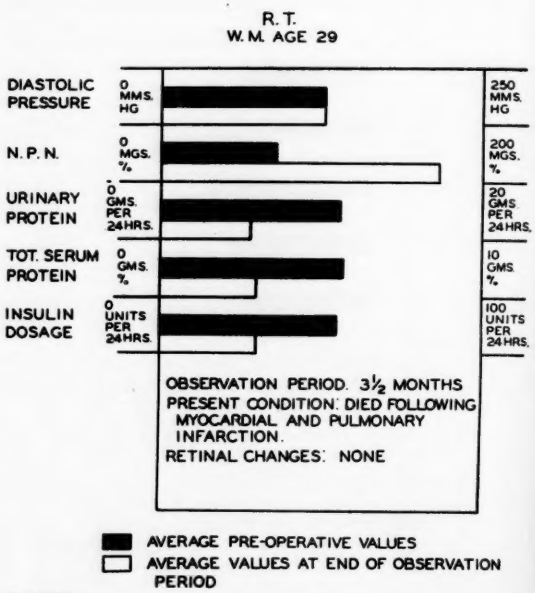

FIGURE 8

ignored all precepts of good diabetic care. Myocardial infarction had occurred at 27 years of age. Chronic edema had been present for one year, and he had been clinically blind for one year due to severe diabetic retinopathy.

The average preoperative blood pressure was 197/125. Before death it averaged 185/125. The average pre-

operative serum nonprotein nitrogen was 69.3 mg. per 100 cc. Before death it reached 170 mg. The preoperative average for urinary protein was 10.9 gm. per 24 hours, and before death it fell to 5.5 gm. The total serum protein, however, fell sharply during this period. The insulin requirement fell from 55 units to an average of 31 units daily after surgery. There was no retinal improvement (figure 8).

CLINICAL ANALYSIS

Obviously, some patients have done quite well, and there has even been evidence of minor reversals in the vascular disease (see figure 2). Others have had no constant or sustained improvement after adrenalectomy. Still others have shown continued progression in vascular disease which resulted in death. The series is too small to permit statistical analysis, but simple comparison may yield some idea as to which patients are likely to benefit from bilateral adrenalectomy.

We have performed only simple clinical observations on this first series. These observations, however, have been performed regularly and frequently. If we average the observed values in the two cases in which there was best response to the procedure (cases 1 and 6) and contrast the initial findings with those in the three cases in which there was little response and eventual fatal outcome (cases 3, 4, and 7), perhaps some prognostic leads can be obtained (figure 9).

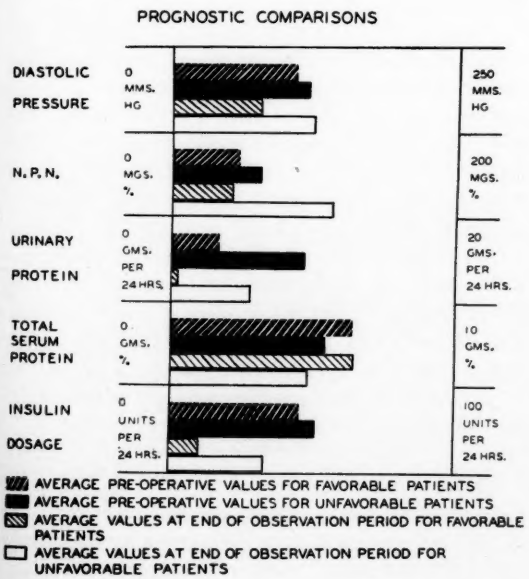
PROGNOSTIC COMPARISONS
DIASTOLIC PRESSURE
0 MMS. HG
250 MMS. HG
N. P. N.
0 MGS. %
200 MGS. %
URINARY PROTEIN
0 GMS. PER 24 HRS.
20 GMS. PER 24 HRS.
TOTAL SERUM PROTEIN
0 GMS. %
10 GMS. %
INSULIN DOSAGE
0 UNITS PER 24 HRS.
100 UNITS PER 24 HRS.
AVERAGE PRE-OPERATIVE VALUES FOR FAVORABLE PATIENTS
AVERAGE PRE-OPERATIVE VALUES FOR UNFAVORABLE PATIENTS
AVERAGE VALUES AT END OF OBSERVATION PERIOD FOR FAVORABLE PATIENTS
AVERAGE VALUES AT END OF OBSERVATION PERIOD FOR UNFAVORABLE PATIENTS

FIGURE 9

The average preoperative diastolic blood pressure level had little prognostic value. The unsuccessful group had slightly higher diastolic pressure than did the successful group. Those patients who responded well in all spheres, however, obtained prompt decreases in blood pressure after adrenalectomy, whereas the other group had no response.

The plasma nonprotein nitrogen averages were not widely different in the two groups. However, the average preoperative value in the satisfactory patients was near the upper limits of normal, whereas in the unsatisfactory group it was considerably above normal.

The amount of urinary protein seemed to be slightly more distinctive. The responsive patients had an average preoperative value of less than 5 gm. daily, whereas the patients with poor response had average values near 10 gm. There was a prompt decrease to near normal values after adrenalectomy in the responsive patients, and a much less satisfactory drop in the unresponsive patients. Serum protein values had no specific prognostic value, and there was little change after adrenalectomy.

The insulin requirement was essentially the same in both groups preoperatively, but in the responsive patients there was a substantial decrease after surgery. This was not marked in the unresponsive patients.

The age of onset of diabetes seemed to hold no prognostic significance. One of our most responsive patients had onset in late middle age, while one of the others was a childhood diabetic. Duration of diabetes was also of little prognostic value.

We can summarize by saying that no single clinical factor that we have observed is of excellent prognostic value. We believe that, in general, successful results have been inversely proportional to the degree of vascular disease. Undoubtedly, when the vascular disease reaches a far-advanced stage of development, adrenalectomy is of no value.

CHANGES IN THE DIABETIC STATE

The patients were all maintained in a state of adrenal sufficiency as determined by clinical symptoms, serum sodium and potassium, and total circulating eosinophile counts. All patients were maintained upon cortisone or hydrocortisone alone. Despite the diabetogenic nature of these steroids, there was a sharp fall in insulin requirement in the successful cases. This is one of the more interesting changes in the diabetic state after adrenalectomy. More important has been the stabilization of the diabetes. Despite the instability of diabetes noted in most patients who have Addison's disease with diabetes,

this behavior has not been noteworthy in our patients. Five patients required multiple daily injections of insulin to achieve close control before adrenalectomy. After adrenalectomy, four of the seven patients could be maintained under close control with a single daily injection of insulin, frequently with a single insulin being utilized. Two of the patients in the older age group are maintained under good control without insulin. In all cases in which diabetes was markedly unstable before adrenalectomy, close control on lower insulin dosages has been possible after adrenalectomy.

DISCUSSION

There is ample evidence that the adrenal cortex plays a significant role in the etiology of degenerative vascular disease in diabetics. Most observers accept the fact that, in these days of multiple insulin types and combinations, insulin hypoglycemia is often periodic, often unsuspected, and very treacherous. Nocturnal hypoglycemia can be found, if carefully sought, in a large percentage of carefully controlled diabetics. This frequently results in rebound hyperglycemia and glycosuria. According to Somogyi,[4] attempts to eradicate these conditions by further increases in insulin dosage lead to more severe hypoglycemia, and then to more severe rebounds of hyperglycemia and glycosuria. We believe that this chain of events leads to "brittleness" and uncontrollability of diabetes and to progressive increases in insulin requirement. The reaction of the adrenal cortex to instability of blood sugar may be at least partially etiologic in the production of these complications of the usual course of diabetes.[5,6] We also believe that the same reaction of the adrenal cortex plays a fundamental part in the etiology of degenerative vascular disease in diabetics.

Engel[7] showed that previous intravenous administration of insulin will significantly decrease the glucose tolerance of both normal and diabetic individuals. Presumably this diabetogenic effect is due to pituitary-adrenal stimulation by the falling blood sugar, with elaboration of diabetogenic adrenal steroids which, secreted in excess of physiologic demand, result in an excessive hyperglycemic response (the rebound phenomenon). This capacity is lost in both hypopituitary and hypoadrenal patients. In these patients intravenous insulin may result in fatal hypoglycemia because of the inability of the pituitary or adrenal to correct the hypoglycemia. This pituitary-adrenal response, then, is a part of the normal mechanism for spontaneous recovery from insulin hypoglycemia.

Some factor which we assume to be in the pituitary-adrenal axis is responsible for progressive insulin resistance following periodic hypoglycemia. Witness the therapy of psychiatric patients who may go into subshock from intravenous insulin doses as low as 10 units, but who may subsequently require 200 or more units to produce the same effect.

Some evidence that high and rising blood sugar levels may produce the same adrenal stimulatory effect has been introduced,[8-12] but has not been fully accepted. There is evidence that relative hypoglycemia—a fall from very high to normal blood sugar levels, for instance—may be as stimulatory to adrenal cortical hyperactivity as is absolute hypoglycemia. The patient on "close" control is subject to the latter type of hypoglycemia, but the patient on "free" control is subject to both types.

It is logical to assume, then, that the patient whose blood sugar undergoes periodic, wide fluctuations is also subject to similar fluctuations in adrenal cortical secretory function. The adrenal secretory functions, under these conditions, might be thought of as in a frequently disturbed state.

The administration of various adrenal steroids in greater than physiologic amounts has resulted in arteriolar degenerative disease.[13-16] Large amounts of the cortical hormones which are most responsive to fluctuations in blood sugar have been used to produce a retinal lesion in animals that is indistinguishable from the lesions of diabetic retinopathy.[17]

Cessation of excessive adrenal cortical adaptive responses and maintenance of the patient on constant, low-dosage replacement therapy would be expected to be palliative of early degenerative vascular lesions. This has proved to be the case in certain patients whose vascular lesions were not excessively far advanced and whose blood pressure could be reduced to normal by adrenalectomy.

The effects of these adaptive mechanisms on pituitary diabetogenic or growth hormone function is not clear at this time. It is possible that adaptive responses in this area of endocrine function may significantly modify vascular function and structure, perhaps more so than is postulated for the adrenal cortical phenomena.

SUMMARY

Bilateral adrenalectomy has been undertaken in seven cases of diabetes with retinopathy and other evidences of advanced vascular disease. After operation all patients have been maintained upon stabilized adrenal replacement therapy of cortisone or hydrocortisone without em-

ployment of other adrenal steroids. Two patients, observed for 14 and 10 months respectively, have shown remission of vascular degeneration as evidenced by minor reversals in retinal changes, return of blood pressure to normal, decrease in proteinuria and nitrogen retention, and clearance of edema. In three cases, there has been no further progression in the pathological features during 13, 10 and 8 months of observation, and less consistent features suggesting improvement have occurred in these cases. One of these patients died in adrenal insufficiency after leaving the care of our service, having initially shown minor evidences of improvement. Two patients continued to have progression of renal failure after adrenalectomy. One died of a cerebral vascular accident 4½ months after operation, and the other died of pulmonary and myocardial infarctions four months after operation.

In general, favorable results have occurred in inverse proportion to the severity of degenerative vascular changes. Based upon these experiences, certain rough criteria for selection of candidates for adrenalectomy have been established. Patients with evidence of extremely severe vascular and renal deterioration are excluded from consideration. Patients with significant nitrogen retention, who excrete more than 5 gm. of urinary protein daily and who have diastolic blood pressures above 120 mm. of mercury are excluded.

Theoretical reasons for believing that abnormal adrenal cortical function resulting from uncontrolled diabetes is pathogenic for vascular degeneration have been discussed.

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DISCUSSION

GEORGE J. HAMWI, M.D., *(Columbus, Ohio)*: At Ohio State, approximately two years ago, we entered upon the same approach to the treatment of diabetes. Adrenalectomy has been performed in two cases. Subsequently, treatment with cortisone and sometimes Doca (desoxycorticosterone) has been given to prevent symptoms of adrenal insufficiency. Clinical improvement has been manifested by ability to work following and preceding invalidism, disappearance of evidence of retinopathy and disappearance of edema. There has also been improvement shown by observation of the serum proteins through studies of the electrophoretic pattern and paper chromatography.

SAMUEL SOSKIN, M.D., (*Los Angeles*): I should like to know some of the progressive changes described. I wonder whether the thyroid function has been followed over the period. Is it possible that some drop in total metabolism might account for some of the changes?

JAMES T. WORTHAM, M.D., (*Little Rock*): I think we can probably both answer, Dr. Soskin, that our patients have been rather routinely followed by protein-bound iodine levels. We have not measured basal metabolism; we have given up metabolism tests. We have found no change as far as protein-bound iodine evaluation is concerned.

GEORGE J. HAMWI, M.D., (*Columbus*): We have also done tests of thyroid functions. There is apparently no change.

HENRY T. RICKETTS, M.D., (*Chicago*): I should like to quarrel a little with the opinion of both authors that ablation of the adrenals is the factor that accounts for greater stability of diabetes. This is in direct conflict with a common observation on spontaneously adrenal-deficient patients with diabetes, who are notoriously unstable and highly sensitive to insulin.

I wish the authors could reconcile these two points of view for us.

ALEXANDER MARBLE, M.D., (*Boston*): I should like to comment briefly regarding the point that by the injection of cortisone one can produce in animals renal and retinal lesions similar to those seen in diabetes. During the past year we have attempted to do this by the giving of cortisone to both normal and alloxan diabetic rabbits maintained on diets deficient in vitamin B_{12}. To date we have not been successful in producing or, at least in demonstrating, retinal lesions. Certain changes have been observed in kidney glomeruli but these have been far from extensive and bear only a limited resemblance to the lesions characteristic of intercapillary glomerulosclerosis. Further work is indicated and this may be more fruitful, but at the moment our results indicate that it is not easy to reproduce by means of cortisone the lesions of the eyes and kidneys seen in human diabetics.

The dose and period of administration of cortisone, the type of rabbits and similar factors may well play a part in the results secured.

JAMES T. WORTHAM, M.D., (*Little Rock*): With regard to Dr. Ricketts' discussion, naturally we thought about the experience with patients with diabetes and Addison's Disease, before we attempted this. However, you know Addison's Disease is a highly variable syndrome; sometimes predominantly hypoglycemic and sometimes predominantly hyponatremic, sometimes neither and sometimes both.

I will say this. I am sure our patients were totally adrenalectomized. We have autopsied three; there was no remnant of adrenal tissue. In these cases I stand on the fact that they are much more stable.

GEORGE J. HAMWI, M.D., (*Columbus*): In regard to the stability of diabetes after adrenalectomy, our patients required as much insulin as before. Occasionally hypoglycemic shock occurred. Actually, I cannot say that the stability of the diabetes has changed particularly following the procedure.

Role of Insurance Examinations in the Detection of Diseases

Within the past few years there has been a tremendous surge of interest in the periodic health examination for the detection of diseases. I think it may be stated unequivocally that by far the greatest single instrument in the detection of illness has been the medical examination of applicants for life insurance. Such disorders as diabetes and hypertension do their damage silently and undermine health over a period of many years before clinical complications emerge. More commonly than not, the first awareness an individual has of glycosuria or elevated blood pressure comes from an unexpected finding on his health examination for life insurance. Disconcerting though this may be to the applicant, it nonetheless starts him on the path to correct medical measures many years earlier than would otherwise have been the case. I think you will all agree that a great job in public health has been and is being accomplished by the procedure of medical examination for life insurance which channels disease in its early, preventable stages to proper medical care. Diabetes and hypertension are perhaps the two most common and most important instances I can cite of the preventive medicine function in insurance, but there are further illustrations, such as the detection of extrasystoles or a heart murmur which send many an insurance applicant on his way to the internist for evalution of his cardiovascular status. Chest X rays, which are required for insurance underwriting in certain instances such as policies in large amounts, elicit many unexpected findings.

. . . . Obesity is not apt to trouble the corpulent applicant, except for some esthetic remorse, until he finds that the extra pounds cost extra dollars in terms of insurability. When confronted with the hard fact that he is not considered a good risk from the point of view of longevity, the obese applicant has an incentive to seek medical attention which he previously lacked. All these then are illustrations of the public health or preventive aspect of life insurance. Although the facts are evident, it has been a surprise to me how the important role of life insurance in the public health of our nation has been quite totally ignored.

From "The Internist and Life Insurance" by Harry E. Ungerleider, M.D., New York, N. Y., *Annals of Internal Medicine* 41:124-30, July, 1954.

Adrenalectomy in Human Diabetes

Clinical and Chemical Study of Bilateral Total Adrenalectomy in a Case of Advanced Intercapillary Glomerulosclerosis

Helen Eastman Martin, M.D., and Mary Lu Wilson, A.B., Los Angeles

The possibility of securing favorable results from adrenalectomy in diabetic vascular disease was suggested to us by a previous report[1] of (1) improvement of malignant hypertension and retinitis following adrenalectomy in a young woman with diabetic nephropathy, (2) the occasional dramatic alteration of the course of hypertension, particularly the malignant form, following adrenalectomy;[2-4] and (3) a suggested adrenal influence on certain types of proteinuria in the rat.[5-9] The following report gives our experience with bilateral total adrenalectomy in one case of diabetes with advanced intercapillary glomerulosclerosis.

HISTORY

R. Mc F., a 28-year-old housewife, was referred by her physician to the Los Angeles County Hospital on June 30, 1952, for treatment of anasarca.

A diagnosis of diabetes had been made 15 years prior to entry because of symptoms of thirst, frequency, and pruritus. Since that time she had been in fair diabetic control and had never been in diabetic coma. At the time of entry she was taking 25 units of NPH insulin daily.

Six years prior to entry, following a spontaneous abortion, the patient developed frequency, burning, pain in the costovertebral angle, and fever. She was told that she had a kidney infection, for which she received antibiotic therapy. She had similar episodes for the next four years. Two years before entry she delivered a stillborn infant between the seventh and eighth months of pregnancy.

During the next two years, she noted swelling of the ankles, which gradually increased in severity. For eight or nine months, she also noted swelling of the abdomen and eyelids, which increased markedly with each menstrual period. At the time she first noted swelling of the ankles she was told that her blood pressure was elevated. There was no shortness of breath. There was increasing fatigue, so that she was almost incapacitated during the six-month period prior to admission. She had had occasional hematuria for one year. At no time had she experienced any disturbance of vision. One brother had died of diabetes.

PHYSICAL EXAMINATION

Physical examination revealed a pale young woman who appeared chronically ill and showed generalized edema. The temperature, pulse, and respiration were normal. The blood pressure was 180/100. The eyes showed no abnormalities of the pupillary reflex, cornea, lens, or vitreous. There were many punctate and flame-shaped hemorrhages in all quadrants of both eyes, but no hard exudates. There was moderate dilatation and beading of the veins, but little change in the arteries. There was no significant enlargement of the heart on percussion. The heart rate was regular. No murmurs were heard. The lungs were clear on auscultation and percussion. No organs or masses were felt in the abdomen. There was slight tenderness in the right upper quadrant but none in the costovertebral angle. Pelvic and rectal examinations revealed no abnormalities. Neurologic examination was negative. There was marked pitting edema in the lower extremities and abdominal wall.

LABORATORY REPORTS

The urine contained 10 to 15 gm. of protein per 24 hours; the urinary sediment contained many coarse and finely granular casts. The hemoglobin was 15 gm. and the white cell count 8800, with 72 per cent neutrophils. The electrocardiogram was normal except for low voltage. The electroencephalogram was normal. A chest film showed the lungs to be clear and the heart of normal size.

The renal clearance tests on three occasions were as

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follows: November 1950, endogenous creatinine clearance, 32.8 cc. per minute. (At this time Dr. Richard Lippman also found the urinary protein 3.5 gm. per 24 hours; urinary sediment—rare casts, rare oval fat bodies, and occasional clumps of pus cells, a moderate number of red cells and rare blood casts; total serum proteins, 4.85 gm. per 100 cc., serum creatinine, 1.56 mg. per 100 cc.): July 17, 1952, creatinine clearance, 43.1 cc. per minute and 38.0 cc. per minute; renal plasma flow, 304 to 325 cc. per minute: August 6, 1952, inulin clearance, 30.1, 27.3, 32.3 cc. per minute; renal plasma flow, 300 to 328 cc. per minute.

The patient and her husband were aware of the hopeless outlook of her disease at the time she was referred. The hazards and possible beneficial effects of adrenalectomy were explained to them and they both consented to the procedure.

COURSE PRIOR TO ADRENALECTOMY

In preparation for adrenalectomy the patient was treated vigorously to relieve the edema (table 1). In two and a half weeks, with the use of large amounts of salt-poor human albumin intravenously, mercurial diuretics, carboresin, and a low sodium diet, she lost 23 pounds (183 to 160 pounds). During this period the blood nonprotein nitrogen level rose from 33 to 77 mg. per 100 cc., presumably because of excessive sodium loss and decrease of overhydration. The serum albumin rose from 1.9 gm. to 3.0 per 100 cc. The urinary protein output also increased from 10-15 gm. to 20 to 38 gm. per 24 hours during periods when albumin was given intravenously.

ADRENALECTOMY

Bilateral total adrenalectomy was performed by the lumbar approach on August 9 by Dr. C. J. Berne, following preparation with cortisone (50 mg. given intramuscularly every six hours for five days and Doca (3 mg. intramuscularly) just prior to surgery. The surgical procedure was uneventful, with no significant change in pulse rate or blood pressure.

The adrenal glands were normal on gross and histologic study. Needle biopsy of the right kidney was performed at the time of operation. Dr. Hugh Edmondson gave the following report on the microscopic sections of this material: "Many of the glomeruli, roughly one-fourth of those seen in the biopsy specimen, are hyalinized. Only an occasional glomerulus appears normal. The remainder show varying degrees of thickening of the capillary walls, associated with a fairly uniform increase in the number of endothelial cells. No typical globoid lesions of intercapillary glomerulosclerosis are noted. A moderate degree of subendothelial hyaline change is present in some of the afferent arterioles. Similar change is noted in the parietal layer of Bowman in an occasional nephron. The histologic changes noted are suggestive of the diffuse form of intercapillary glomerulosclerosis, associated with which is a degree of endothelial proliferation usually not seen in this disease. This might be interpreted as glomerulonephritis except that it is extremely rare that these two diseases occur simultaneously in diabetics."

COURSE FOLLOWING ADRENALECTOMY

Clinical Features (*table 2*)

The patient was ambulatory within three days following operation and the incisions were well healed within ten days. She was discharged from the hospital in three and one-half weeks, feeling well and with minimal edema (weight 158 pounds), on a dosage of 25 mg. of cortisone orally and 30 units of NPH insulin daily. The blood pressure on discharge was 150/90. The nonprotein nitrogen was 50 mg. per 100 cc.

The patient was seen at approximately weekly intervals as an outpatient. During the next eleven months she was admitted to the hospital four times. The important conditions during each stay were as follows: September 7-9, 1952: severe hypoglycemic reaction with deep stupor. December 15-30: headache, nausea, and vomiting. March 5-8, 1953: abscess of lip, with cellulitis of face. March 12-20: severe headache, malignant hypertension. May 31-July 1: infected callus on foot, infected lip and severe headache, malignant hypertension.

On July 4 the patient was again brought to the hospital but she was dead on arrival. Three hours earlier there had been a sudden onset of paralysis of the legs which rapidly ascended to involve the arms, following which there was difficulty in breathing and vomiting.

Except for minor problems of adjusting the cortisone and insulin dosage the patient had been fairly well for the first four and a half months postoperatively. During the next six months there was slow deterioration until death. Because of a general rise in the serum potassium level (6.3 to 7.6 mEq/L.) occasional hyponatremia (118 to 126 mEq/L.) and severe muscle aching, the dose of cortisone was increased to 50 mg. daily and occasionally small doses of desoxycorticosterone (2 to 3 mg. of Doca) were given intramuscularly. With this therapy the blood pressure rose progressively to as high as 230/140, and intractable headaches appeared. "Cotton

TABLE 1

Chemical studies prior to adrenalectomy

1952		Chemistry									Treatment/24 hours				
		Urine/24 hours				Blood									
Date	Sugar gm.	Protein gm.	Sodium mEq.	Calcium mEq.	Magnesium mEq.	NPN mg. 100 cc.	Na mEq/L.	Serum K mEq/L.	Albumin gm. per 100 cc.	Weight lbs.	Albumin* I.V. gm.	Mercuhydrin I.M. cc.	Carboresin gm.	Cortisone I.M. mg.	Estimated sodium intake mEq.
							Base line period								
7-7	0	12.3	22.5	0.16	5.70	53									
7-8	0	10.8	23.0	0.08	4.66					178					
7-9	0	12.1	37.6	0.07	6.46				1.9						44-66
7-10	0	14.5	38.0	0.23	6.70										44-66
7-11	0	13.8	28.9	0.25	6.25										44-66
7-12	0	10.3	22.4	0.26	5.40					175½					44-66
7-13	0	12.3	28.5	0.26	6.44										44-66
7-14	0	13.3	29.2	0.00	6.42	39									44-66
7-15	0	11.4	17.0	0.06	5.50					179					44-66
7-16	0	12.1	24.1	0.00	6.02	33	136	5.1							44-66
															44-66
							Diuretic Therapy								
7-21	0	22.6	82.0	0	8.40										
7-22	0	23.7	79.5	0	7.40					183½	25				
7-23	0	25.6	80.5	0	6.90				2.0		25				44-66
7-24	0	30.8	62.7	0	5.85						25				44-66
7-25	0	30.7	92.0	0	7.86						25				44-66
7-26	0	34.0	82.5	0	6.20				2.8		25				44-66
7-27	0	38.0	89.7	0	5.78										44-66
7-28	0	34.6	218	0.40	8.28										44-66
7-29	0	32.0	73.6	0	5.70							1	60		44-66
7-30	0	29.2	92.0	0	6.45					178			60		44-66
7-31	0	25.6	304.0	0.80	11.5	40	144	5.4					60		44-66
8-1	0	24.3	63.7	0.00	5.5					172½		1	60		44-66
8-2	0	22.1	65.2	0.05	3.83					168¾			60		44-66
8-3	0	21.1	70.0	0	4.24					167			60		44-66
8-4	0	25.8	336	1.0	9.95					166½					44-66
8-5	Trace	28.7	31.2	.05	2.49	46	143	5.8	2.9	165	25	1		200	44-66
8-6	47	23.4	15.6	.11	1.22					160½	25			200	44-66
8-7	65.4	27.4	149	4.03	7.10	60	137	3.9		160¾	25			200	13
8-8	10.3	23.4	11.8	0.91	1.88	77	140	5.3	3.0	160		1		200	13
														200	13

*Salt-poor human albumin

TABLE 2

Clinical Features*

Mo.	Drugs: Insulin, subcutaneously units	Drugs: Cortisone (orally)† mg./24 hrs.	Drugs: Albumin I.V.‡ gm.	Drugs: Doca I.M. mg.	Drugs: Mercuhydrin I.V. or I.M. cc.	Drugs: Na in diet§ mEq.	Clinical status: Wt. in lbs.	Clinical status: Edema‖	Clinical status: Blood pressure range	Clinical status: Headache‖	Other features
							Preadrenalectomy				
1	35-40 NPH	0	225			13–66	183–166½	4+ to 2+	180/100	0 to 1+	
							Postadrenalectomy				
1	10 regular 30 NPH	25-50	75			109	166–158	2+ to + trace	165/85	0	
2	10 regular 35-40 NPH	19-25				109	158–151	2+	160/82 to 200/110	0	Some periods of weakness and diarrhea.
3	15-25 regular 35-45 NPH	25-37.5				109	150½–154	1+ to 2+	148/100 to 190/120	0	Some periods of weakness and diarrhea.
4	15 regular 35 NPH	37.5				109	155½–158½	4+	190/120 to 220/140	0	Felt well most of month.
5	15 regular 40 NPH	37.5	75	3 4x	2–1x 1–1x	109	164–?	4+	240/125 to 160/ 80	2 to 4+	Nausea and vomiting.
6	10-15 regular 25-35 NPH	37.5		3 3x		109	162–151	1+ to 0	169/80 to 220/120	0 to 4+	Muscle aching.
7	20 regular 40 NPH	37.5-50		3 3x	1 1x	109	154–153	0 to 1+	200/120	0 to 4+	Muscle aching.
8	20-25 regular 40-45 NPH	50	75	3 2x	1 2x	109	156½–149		220/140 to 170/88	2+ to 4+	Muscle aching. Cellulitis–lip.
9	20 regular 40 NPH	50				109	156–161½	1+ to 0	200/130 to 220/140	0 to 4+	Skin infections, chronic sore throat, muscle aching.
10	20 regular 35-40 NPH	50	75	3 1x	2–1x 1–1x	109	165–157½	2+	200/130 to 260/140	4+	Cellulitis–lip, cellulitis–foot, muscle aching, chronic sore throat.
11	10-25 regular 30-40 NPH	50-25	50			109	155–138	0	230/125 to 145/92	1+ to 2+	Chronic sore throat. Nausea and vomiting.

* Does not include preparation for adrenalectomy with cortisone, doca, etc. (see table 1) or all acute changes in therapy during hospitalizations.

† Cortisone given orally twice daily, except before operation.

‡ Salt-poor human albumin.

§ Estimated average sodium intake. Intake occasionally lower or higher (44-189 mEq.)

‖ Graded 0 to 4.

|| Graded 0 to 4.

TABLE 3

Correlation of therapy and chemical tests*

Time	Drugs		Urine		Urine electrolytes mEq. per 24 hours					Blood NPN	Serum Albumin/ globulin	Serum Electrolytes mEq. per L.						
Week	Cortisone† mg./24 hrs.	Insulin units/24 hrs.	Protein gm./24 hrs.	Sugar gm.	Na	K	Ca	Mg	PO_4	mg./ 100 cc.	gm. per 100 cc.	Na	K	Ca	Mg	Cl	HCO_3	PO_4
							Preadrenalectomy											
4	0	35 NPH	12.3	0	23	41	0.2	5.7		53	1.9/1.7							
3	0	35 NPH	12.1	0	24	57	0.0	6.0	19.8	33		136	5.1	3.65	1.9	110	27	2.82
							Postadrenalectomy											
3	25	35 NPH	14.2	0	111	75	0.2	7.0		53	2.3/1.4	148	5.6	4.7	2.0		27	
7	37.5-25	30 NPH	18.5	100	189	98	0.0	7.3		62	2.5/1.8	124	5.8					
11	37.5	35 NPH	15.3	22	183	92	2.7	8.5	65.4	54	2.6/1.6	139	6.0	4.4	1.7	117		3.08
17	37.5	15 regular 35 NPH	16.2	36	100	68	0.0	6.8		66	2.5/1.8	134	6.1		1.93			
20	25	55 regular 25 NPH	5.5		88	48				66	1.9/1.6	118	5.2				16	
25	37.5	15 regular 35 NPH	16.5	18	147	77				73	3.0/1.8	134	6.7	4.5				
26	37.5	15 regular 35 NPH								69	2.9/1.4	126	7.6					
29	50	25 regular 45 NPH	16.2	19	81	83				70	3.0/1.6	126	6.7					
34	50	25 regular 40 NPH	15.5	50	101	90				84	3.5/1.7	136	6.8					
36	50	20 regular 40 NPH	18.7	55	66	107	0.7	5.4	59.5	87	3.1/1.4	138	6.2				22	
40	50	20 regular 35 NPH	18.8	15	90	73	0.0	9.8	52.3	76	2.6/1.7	138	5.8					
42	50	20 regular 35 NPH	30.8‡	45	110	82				77	2.9/1.5	135	5.7					
43	50									73	2.4/1.7	145	5.2	3.7		109	25	3.0
47	25	15 regular 35 NPH								87	3.3/2.0	134	6.5			100	18	

* Chemical studies were done weekly. The determinations listed represent the general pattern of results at varying periods of the course.

† Cortisone orally twice daily.

‡ Concentrated salt-poor human albumin intravenously four days prior to this test.

wool" type exudates appeared in the fundi, with increased dilatation of the veins and marked arteriovenous nicking. Periods of nausea and vomiting also occurred, with development of diabetic acidosis and ketosis.

There was a slight increase in pigmentation when the patient received 37.5 mg. of cortisone daily. When the dosage was increased to 50 mg. there was a striking increase in pigmentation similar to that seen in severe adrenal insufficiency.

Since the patient had developed a malignant hypertension on 50 mg. of cortisone, the daily dose was gradually reduced to 25 mg. over a two-week period in June 1953, with a parallel fall in blood pressure from 260/140 to 145/92, and concomitant loss of edema, and headache. The body weight during this period dropped from 163 to 138 pounds. She was discharged on July 1 at which time nonprotein nitrogen was 87 mg. per 100 cc. the potassium 6.5 mEq/L., the sodium 130, the chloride 100, the serum bicarbonate 18, the serum albumin 3.3 gm. per 100 cc., and the globulin 2 gm. Except for weakness she felt well and was eating well. On the morning of July 3 she had severe aching of the legs and general weakness. The morning dose of cortisone was increased from 12.5 to 25 mg. At 10:30 that evening she was unable to move her legs. By 11 p.m. she could not move her arms and a 25 mg. dose of cortisone was ordered. Half an hour later she was vomiting and had respiratory difficulty. She was then rushed to the hospital, but was dead on arrival at 1 a.m. Permission for autopsy was refused.

There is little doubt that this patient died of adrenal insufficiency with hyperkalemia and paralysis of the respiratory muscles. We were in a difficult therapeutic impasse between adrenal insufficiency when the cortisone was decreased, with augmentation of the hyperkalemia and azotemia by the severe grade of renal impairment, and malignant hypertension and edema when the cortisone was increased.

CHEMICAL TESTS

Prior to adrenalectomy there was a marked reduction of 24-hour urinary sodium output—under 40 mEq. on an estimated daily intake of 44 to 66 mEq. Following mercurial diuretics, the maximum excretion reached 336 mEq. in a 24-hour period. After adrenalectomy the output increased dramatically, ranging from 66 to 189 on an estimated average intake of 43 to 155 mEq. of sodium daily. The urinary potassium excretion ranged from 53 to 107 mEq. per 24 hours throughout the entire period after adrenalectomy. The dietary potassium intake was unfortunately not controlled.

The serum sodium and potassium fluctuated considerably depending on the adrenal replacement therapy, with serum potassium levels ranging from 4.5 to 7.6 mEq/L. and serum sodium levels from 118 to 148 mEq/L. The serum chloride levels when tested usually showed moderately increased values (110 to 115 mEq/L.). The serum bicarbonate until a few days before death was usually normal, except when ketosis was present. The serum phosphate levels were within the normal range throughout the course. There was a marked increase in urinary phosphate excretion following adrenalectomy. There was little significant change in levels of serum calcium or magnesium except in two serum calcium levels. The serum calcium was 3.65 mEq/L. on one occasion prior to adrenalectomy. At this time the serum albumin level was 1.9 gm. per 100 cc. The serum calcium one month before death was also low, 3.7 mEq/L. At this time the serum albumin level was 2.4 gm. per 100 cc., but there was only moderate edema. There was no significant increase in urinary calcium output following adrenalectomy except on one occasion. However, infrequent tests of urinary calcium were done. The urinary magnesium output fluctuated within the normal range (4 to 8 mEq. per 24 hours), except during diuretic therapy, when higher outputs usually occurred.

The nonprotein nitrogen level always rose slightly with too much sodium loss, whether due to mercurial diuretics, inadequate adrenal replacement therapy, and/or inadequate sodium intake. It only rose, however, from a preadrenalectomy level of 53 mg. per 100 cc. to 87 mg. a few days before death.

With large amounts of concentrated salt-poor human albumin, it was possible to increase the serum albumin levels from a low of 1.8 gm. per 100 cc. to a high of 3.5 gm. Most of the albumin given intravenously, however, was lost gradually in the urine over a period of four to five days following injection. There appeared to be some slight over-all increase in serum albumin levels after adrenalectomy, despite a slightly greater urinary protein loss.

It had been hoped that the adrenalectomy would decrease the proteinuria. Before adrenalectomy the urinary protein output varied from 10 to 15 gm. per 24 hours. After adrenalectomy (except for periods when salt-poor albumin was given) the urine protein usually varied from 10 to 19 gm. per day. There was one period when the output dropped sharply to 5 to 10 gm.

The insulin requirement varied in a manner that in general paralleled the increases or decreases in cortisone.

Thus, before adrenalectomy the patient was well controlled on 35 units of NPH insulin daily. With 50 mg. of cortisone daily she required 40 to 45 units of NPH insulin, plus 20 units of regular insulin. Even with this increased insulin dosage glycosuria was not controlled.

DISCUSSION

Since we undertook the adrenalectomy in this patient, a preliminary report has been made on 7 diabetic patients subjected to adrenalectomy,[10] followed by a more detailed report[11] with results and indications for selection of cases. Two more cases are mentioned in the discussion of the original paper.[12] In addition to the 11 reported cases, including our patient,[1,11] we know of several other cases, not as yet reported,[13] in which adrenalectomy has been done for diabetic vascular disease. Hypophysectomy has also been done for several patients with diabetic vascular disease, with favorable results.[14] From all the results obtained, it appears that patients with advanced vascular disease and marked proteinuria do poorly. Five of the 11 reported cases terminated in death—from adrenal insufficiency in 3 and from vascular or renal failure in 2. The patients who have survived have shown striking improvement of proteinuria, retinitis, and hypertension.

Certain of the results of bilateral adrenalectomy in our patient warrant mention. It was possible to reduce her blood pressure to normal levels if adrenal replacement therapy was minimal and a very mild state of adrenal insufficiency was present. Her renal status, however, would not tolerate this, and there was always a prompt rise in blood nonprotein nitrogen and serum potassium levels.

Generalized dark-brown pigmentation developed in this previously fair-skinned young woman as her cortisone dosage was increased to 50 mg. daily. This is in accord with the reported occurrence of pigmentation following adrenalectomy[15] particularly at the higher dosage levels of cortisone (50 mg. per 24 hours).

As is usual following adrenalectomy, there was a definite increase in urinary sodium excretion. This made the problem of handling the edema somewhat easier. The sodium intake, however, could not be decreased as much as desired due to the degree of hypoalbuminemia, with its associated expansion of extracellular volume.

We obtained no significant change in urinary protein excretion following adrenalectomy except at one period when the serum albumin level was very low. We are unable to explain this drop of urinary protein excretion, however, entirely on the basis of decreased filtration of protein due to the very low serum albumin level, since prior to adrenalectomy the serum albumin was in the same range, with considerably higher urinary protein excretion. It is to be noted that during this period of decreased urinary protein excretion the patient was in a state of mild adrenal insufficiency. This may have been the responsible factor.

It has been suggested[13] that proteinuria would have been decreased in our patient if Doca (desoxycorticosterone) alone had been used for replacement therapy following adrenalectomy. It is of interest in this regard that the diabetic patient reported by Green and his associates received only Doca, whole adrenal extract, and lipoadrenal extract following adrenalectomy, with improvement of blood pressure levels and suggested improvement of renal function. Unfortunately no quantitative urinary protein levels were reported in this study. However, the patients reported by Wortham[11] and Hamwi[12] showed a decrease in urinary protein excretion on cortisone or hydrocortisone therapy alone.

Experimentally, the response of the adrenalectomized rat to Doca and cortisone, as to level of renin proteinuria and development of hypertension, is different. Addis and Boyd[5] observed that adrenalectomy abolished renin proteinuria in the rat and that this could be restored by Doca, cortisone, or adrenal cortical extract. Others[6] have shown that hypophysectomy also abolishes renin proteinuria, and this could be restored by cortisone, but not by Doca or corticotropin. The adrenalectomized rat on a sodium-restricted diet develops marked hypertension when cortisone is given, and no hypertension if Doca is given. However, when the diet is liberal in sodium there is less hypertension in the adrenalectomized rat on cortisone than on Doca.[16] Further exploration of this problem of the differential response of proteinuria and hypertension to Doca and cortisone is required in man.

Despite the fatal outcome of our patient, we believe that adrenalectomy in other diabetic patients with less advanced vascular and renal disease should be done, since any approach which offers hope of even partial alleviation of symptoms or signs is warranted in view of the present hopeless outlook.

SUMMARY

The case of a 28-year-old housewife with diabetes and advanced intercapillary glomerulosclerosis is presented with a detailed clinical and chemical study prior to adrenalectomy and for eleven months thereafter.

The patient was maintained on 25 to 50 mg. of cortisone orally per day with infrequent small doses of

desoxycorticosterone (3 mg. Doca intramuscularly). The urinary protein excretion was not decreased by the adrenalectomy on this replacement regime. The urinary sodium excretion was increased by the adrenalectomy. Malignant hypertension developed when she received 50 mg. of cortisone daily.

Death occurred from adrenal insufficiency, with hyperkalemia and rapidly ascending muscular paralysis when the cortisone dosage was reduced from 50 to 25 mg. per day, in order to relieve the malignant hypertension that had developed.

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Thyroid Stimulation in Diabetes Mellitus

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Relationships between human thyroid glandular alterations and diabetes mellitus have received the most attention in hyperthyroidism. Hyperglycemia and glycosuria attendant on thyrotoxicosis may lead to false diagnoses of diabetes unless strict criteria are observed. Also it is known both from clinical and experimental studies that hyperthyroidism exaggerates and myxedema may ameliorate the disturbed carbohydrate metabolism of some diabetics.[1]

Examinations of thyroid glands by routine pathological methods have failed to reveal any significant changes in diabetic persons.[2] Suggestive differences observed in experimental studies of diabetes led to a search for a more accurate quantitative morphologic method of assaying thyroid functional activities.

In 1934 Goormaghtigh and Thomas,[3] and Thomas[4] described the histophysiology of human thyroid glands in a qualitative manner and provided a classification of four thyroid cell types. According to these authors each cell type had certain histophysiologic functions of colloid resorption, slow or active secretion for storage, or were in resting states. The cell types were recognized as differing chiefly in their activities, each correlated with a certain morphologic appearance. Thyroid cells evidently often underwent metamorphosis in response to various stimuli.

We[5] recently developed a thyroid cell mapping method as a quantitative application of the work of Goormaghtigh and Thomas. By its use an accurate numerical and proportional accounting of the thyroid cell types was achieved. The method has already been employed in studying the thyroid glands of about 100 persons, using surgical or autopsy material. Findings of particular interest in the thyroid glands of patients with diabetes mellitus form the basis of this report.

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MATERIAL

As stated in the article in the thyroid cell mapping method,[5] a control series was compiled comprising 30 thyroid glands removed at autopsy from persons without evident endocrine disease. Cases were selected otherwise only to secure equal sex distribution and to represent all age groups from 23 to 86 years. Cases of sudden or accidental death were not available. Surgical specimens of primary thyroid hyperplasia were similarly mapped.

Forty-two thyroid glands were examined from autopsy material of patients with diabetes mellitus, obtained from the files of the New England Deaconess Hospital. Cases were selected so as to be divided fairly evenly by sex, with 23 women and 19 men, and to be representative of each decade from the third to the ninth. Otherwise the material for study was unselected.

All the specimens had been fixed in Zenker's solution, paraffin embedded and stained by eosin methylene-blue or hematoxylin and eosin. Some faded slides were decolorized and restained by a modified Masson method. Scrutiny of slides revealed some additional cases too poorly fixed for cell counts, and these thyroids, whether control, diabetic or hyperplastic, were discarded.

METHODS

Details of the thyroid cell mapping method are published elsewhere.[5] In brief, by the Bazin cartographic squaring method, using a net reticule in the microscope eyepiece and a magnification of 215 times, thyroid follicular outlines and dots designating the locations of epithelial nuclei were drawn on squared graph paper. From a random marked point 30 horizontal and 7 vertical fields each 200 μ square were reproduced, giving a total mapped area of 8.4 sq. mm. An attempt was made to include representative numbers of follicles of different sizes. After the guide drawing was prepared, at a magnification of 970 times with an oil immersion lens each cell was identified and a code symbol designating the thyroid cell type was drawn over each dot marking a nuclear location (figure 1). Finally with a laboratory counter the cells were tabulated and the percentages of each were calculated. The total cell counts averaged 10,000 per gland.

The cell types adopted from Goormaghtigh and

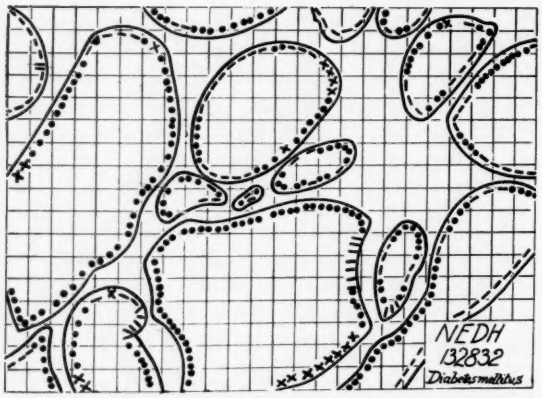

FIG. 1. Portion of a thyroid map from a diabetic man, aged 56 years. About one-fiftieth of the entire mapped area is reproduced. Code symbols employed are a dot for each Type I cell, perpendicular line for Type II, trapezoid for Type III, parallel line for Type IV and X for degenerated cell.

Thomas,[3] and Thomas[4] have distinguished cellular characteristics, illustrated in figure 2. The functional characteristics ascribed to them by the original authors were as follows:

Type I, cuboidal, slowly secreting (figure 2, I). There is bipolar secretion, mainly through the apical pole, leading to colloid storage, and probably to a lesser extent through the basal pole into circulating body fluids. Type I cells predominate in normal thyroids and are the only cells normally present up to 10 to 14 years of age.

FIG. 2. Morphology of typical Type I cuboidal, Type II columnar, and Type III, trapezoidal thyroid cells, with arrows indicating their characteristic functions of secretion or resorption. Follicular spaces are at tops of the cells shown, and sinusoids below cell bases. Copied from Thomas[4] with permission.

Type II, columnar, resorptive (figure 2, II). Active reabsorption of follicular colloid occurs, with its intracellular re-elaboration and active secretion through the basal pole into the milieu interne. Such cells are notably increased in hyperthyroidism, make up the Sanderson polsters indicative of localized resorptive hyperactivity, and occur in the newborn thyroid, which reflects the maternal hormonal stimuli.

Type III, trapezoidal, actively secreting (figure 2, III). They elaborate colloid droplets and secrete them into the follicle for storage. Any situation attended by restoration of follicular colloid finds Type III cells increased.

Type IV, endothelioid, hypoactive. Such cells slowly secrete colloid into follicles. They are almost at rest, but can rapidly metamorphose into other cell types. This cell type predominates when hormonal output is abnormally low.

Degenerated cells with pyknotic or ruptured nuclei could not readily be classified, except in retrospect, and were recorded as such. It is re-emphasized that the thyroid cell types reflect different functional activities, that there is labile thyroid responsiveness to various stimuli, and that the thyroid cell map represents neither a past nor a prospective secretory cycle but only its actual state.

RESULTS

From the control series previously reported of 30 human thyroid glands in average states of activity, the following data were obtained. Type I cells had a mean representation of 49.18 per cent, with a range of 27.95 to 78.05 per cent. Type II cells averaged 0.47 per cent, ranging from 0.01 to 1.38 per cent, and only a single control case had over 1 per cent Type II cells. Type III cells had a mean of 0.23 per cent, ranging from none to 2.54 per cent. The Type IV cell mean was 23.65 per cent with a range of 5.20 to 47.30 per cent. Degenerated cells ranged from 5.17 to 65.57 per cent, with the mean 26.46 per cent. Only in 8 of 30 cases did the nonviable cells exceed one-third. Increased postmortem degeneration was to be expected in autopsy material.

The major difference recorded in primary hyperthyroidism was the greatly increased proportion of Type II cells; the mean was 25.22 per cent and range 11.43 to 37.71 per cent. This was over fifty times the average percentage of Type II cells in the control series. Also Type IV cells were reduced; the mean was 14.57 per cent, or a little less than two-thirds of the average control percentage. Nonviable cells in the surgical material averaged 6.28 per cent, or about one-fourth those found in autopsy specimens. The results conformed closely to the pathologic diagnoses, which at the New England Deaconess Hospital routinely include estimations of early, moderate, or late involution of primary thyroid hyperplasias.

In the series of cell counts of 42 thyroids in cases of diabetes mellitus (table 1), the outstanding finding was that in every case Type II cells were present in increased numbers, from over 1.18 per cent to as high

as 10.39 per cent. The mean was 4.47 per cent, almost exactly ten times the mean control Type II percentage. Type I cells ranged from 26.14 to 75.16 per cent, mean 51.64 per cent. Type III cells were present from none to 3.21 per cent, mean 0.51 per cent. Type IV cells had a range of 2.99 to 42.40 per cent, mean 19.94 per cent. Degenerated cells ranged from none to 61.23 per cent, with the mean 23.42 per cent. Only 9 of 42 cases had over one-third degenerated cells.

Increased numbers of Type II thyroid cells, according to the histophysiologic theory of Goormaghtigh and Thomas, indicate that an increased colloid resorption and an accelerated hormonal secretory activity must be characteristic of diabetes mellitus, regardless of the patient's age or sex. An investigation of the basis of this inferred overactivity suggested the blood sugar level as a possible responsible factor.

On this account thyroid material was collected from autopsied cases in which the record showed that intravenous glucose therapy had been given shortly before death, and in which there was no clinical or pathologic evidence of diabetes mellitus or thyroid disease. In regard to the latter there was one exception; a thyroid gland from a woman aged 41 years weighed 45 gm. and contained a single fluid-filled cyst 3 cm. in diameter. The necessary clinical information and cell counts are listed in table 2. When the clinical record and nurses' notes did not give the exact times of administration of glucose, the possible outside limits of infusion were recorded.

TABLE 1
Thyroid cell counts in 42 cases of diabetes mellitus

	Age	Sex	Cell Types				
			I	II	III	IV	Degenerated
			%	%	%	%	%
1	22	F	42.55	2.65	0.10	11.49	43.21
2	24	F	53.90	3.65	0.21	9.73	32.51
3	25	F	58.76	7.86	0.32	2.99	30.07
4	27	M	71.65	7.20	0.15	18.65	2.35
5	28	M	58.52	3.27	0.22	25.02	12.97
6	30	M	75.16	4.26	0.04	16.23	4.31
7	31	F	62.60	2.61	0.28	29.65	4.86
8	32	F	49.78	3.20	0.00	35.56	11.46
9	38	F	34.25	1.69	0.33	16.72	47.01
10	41	M	36.93	3.41	0.06	42.40	17.20
11	42	F	49.91	3.73	0.05	20.11	26.20
12	42	M	60.42	6.59	1.47	19.44	12.08
13	45	F	50.91	10.47	1.63	26.63	10.36
14	46	M	54.16	5.70	0.21	22.06	17.87
15	47	F	37.93	3.46	0.09	6.34	52.18
16	50	M	43.45	2.29	0.42	6.79	47.05
17	51	F	65.37	10.93	1.28	7.32	15.10
18	55	F	53.75	3.06	0.08	15.20	27.91
19	56	M	56.48	1.31	0.17	37.31	4.73
20	57	M	41.04	3.73	0.08	39.35	15.80
21	59	F	71.41	2.61	0.41	7.14	18.43
22	59	M	44.56	6.01	0.27	11.00	38.16
23	59	F	48.92	6.47	0.07	17.12	27.42
24	59	F	34.42	2.94	0.77	26.82	35.05
25	61	M	59.30	3.56	0.27	26.59	10.28
26	63	F	58.57	1.18	0.32	13.05	26.88
27	64	F	38.79	2.87	0.04	28.87	29.43
28	65	M	42.63	1.34	0.27	17.70	38.06
29	65	F	51.57	5.17	0.14	13.41	29.71
30	67	F	63.74	1.91	0.26	15.59	18.50
31	68	M	65.20	5.70	1.50	27.60	0.00
32	70	F	48.79	2.82	0.29	22.11	25.99
33	71	F	45.37	3.87	0.36	28.29	22.11
34	71	M	74.05	8.82	0.19	11.65	5.29
35	71	F	46.45	6.64	2.07	17.96	26.88
36	71	M	45.70	5.84	3.21	27.26	17.99
37	74	M	36.36	2.71	0.14	21.91	38.88
38	74	M	61.59	16.39	2.05	9.76	10.21
39	75	F	34.93	1.55	0.25	38.86	24.41
40	79	M	26.14	1.23	0.15	11.25	61.23
41	84	F	62.21	3.81	0.36	14.00	19.62
42	86	M	50.73	3.52	0.86	20.91	23.98
Mean			51.64	4.47	0.51	19.94	23.42

TABLE 2

Nondiabetic cases with intravenous glucose therapy

No.	Age	Sex	Glucose as 5% solution gm.	Hours antemortem	Operation and major disease	Cell types I	II	III	IV	Degenerated
						%	%	%	%	%
1	9	M	15	3-10	Postoperative craniotomy for craniopharyngioma; body weight 32 kg.	43.18	8.08	0.08	15.04	33.62
2	24	M	50	0-4	Postoperative craniotomy for cerebral hemorrhage	60.65	1.50	0.14	11.30	26.41
3	32	M	75	8-12	Postoperative craniotomy for astrocytoma	51.31	5.07	0.27	17.13	26.22
4	41	F	50	6¼	Postoperative exenteration for carcinoma of cervix	56.05	3.31	0.22	18.38	22.04
5	41	M	225	10	Polycystic kidneys, fasting blood sugar 154 mg. %	48.42	2.67	0.58	31.45	16.88
6	45	M	125	10	Postoperative lobectomy for tuberculosis and laparotomy for intestinal obstruction	55.29	2.87	0.14	24.63	17.07
7	51	F	75	8*	Postoperative craniotomy for cerebral infarcts	47.92	3.07	0.42	36.02	12.57
8	52	M	142	4-7	Postoperative craniotomy for cholesteatoma	66.97	4.67	0.19	18.97	9.20
9	54	M	100	2-5½*	Postoperative lobectomy for bullous emphysema	52.41	8.72	0.45	16.71	21.71
10	59	M	50	1-12	Postoperative craniotomy for chordoma	15.40	2.55	0.15	13.30	68.60
11	59	M	75	6*	Postoperative craniotomy for glioma	31.09	1.76	0.38	50.93	15.84
12	60	M	24	5½*	Postoperative cholecystectomy for pulmonary infarcts	40.40	1.91	0.06	52.66	4.97
13	63	F	50	11½*	Adenocarcinoma of colon; fasting blood sugar 124 mg. %	63.92	6.43	0.36	10.22	19.07

* Systolic blood pressure below 100, 12 hours or less before death.

Table 2 indicates that with the administration of glucose in amounts from 24 to 225 gm. from 1 to 12 hours before death, Type II thyroid cells were increased uniformly in the 13 cases studied. With the presence of increased numbers of Type II cells at a post-infusion interval of about 10 hours, in general over 100 gm. of glucose had been administered.

Among the 30 control cases used in the original study of thyroid mapping,[5] 14 were recorded as having received intravenous glucose solutions within 24 hours of death. Most of these patients had received 50 gm. of glucose 12 to 24 hours antemortem (table 3). Evidently within

TABLE 3

Control cases with intravenous glucose therapy and less than 1% Type II cells

No.	Age	Sex	Glucose as 5% solution gm.	Administered antemortem hr.	Major disease	Type II Cells %
1	23	F	50	12	Acoustic neurilemmoma	0.66
2	29	M	75	4*	Postoperative craniotomy, colloid cyst	0.44
3	31	F	50	9†	Carcinoma of stomach	0.18
4	31	M	50	1½‡	Ulcerative colitis	0.23
5	36	M	50	14	Hypertensive cardiovascular disease	0.49
6	40	F	50	7§	Postoperative staphylococcal enteritis	0.45
7	41	F	50	17	Postoperative cholecystectomy; biliary cirrhosis	0.25
8	47	M	75	9‖	Ulcerative colitis; rheumatic myocarditis	0.13
9	52	M	50	15	Postoperative gastrectomy for peptic ulcer	0.73
10	56	M	50	14	Carcinoma of lung	0.75
11	64	M	50	24	Postoperative adenocarcinoma of sigmoid	0.45
12	67	F	50	12	Postoperative adenocarcinoma of sigmoid	0.01
13	74	F	100	16	Postoperative parotid tumor	0.20
14	77	F	25	12	Diverticulitis, hemorrhage	0.56

* Blood pressure 80/70, 3 hours antemortem.
† Blood pressure 96/42, 15 hours antemortem.
‡ Blood pressure not recorded; generalized peritonitis.
§ Blood pressure 68-80/10-50, day of death.
‖ Blood pressure 80/40, last recorded; patient died at end of operation.

12 hours the physiologic effects of 50 gm. of glucose, or about 200 calories, had been dissipated. The five persons in this group who received glucose 9 hours or less antemortem were in shock at this time, and it is doubtful that the glucose was adequately circulated in the body.

Among the 42 diabetic patients, it will be recalled that the mean percentage of Type II thyroid cells was 4.47 per cent, or ten times the mean percentage in the controls. Scrutiny of the distributions of percentages of Type II cells in individual cases revealed a tendency for diabetics to fall into two groups. Twenty-eight cases had Type II thyroid cell percentages of 4.5 per cent or less. The other 14 diabetics had over 5 per cent of these cells. The distribution of cases did not suggest chance variations within a homogeneous group. Instead the presence of some other active stimulus was suggested in the 14 diabetes mellitus cases with over 5 per cent Type II.

On this account all 42 diabetic cases were investigated as to the severity of diabetes; average and range of protamine zinc and regular insulin dosage; average, range, and last recorded blood sugar, plasma or serum cholesterol, blood pressure; duration of diabetes, and cause of death. No differences were recognized between the two diabetic groups.

All available microscopic slides from the 14 complete diabetic autopsy examinations were reviewed. No regular or significant differences between the two groups of diabetics were observed in the heart, lungs, spleen, pancreas, liver, adrenals, kidneys, or genitalia. In the anterior pituitary lobes differences in the appearance of basophils were detected. In the diabetic group with over 5 per cent Type II thyroid cells, the basophils were enlarged with an abundant finely granular or vacuolated cytoplasm. These sparsely granulated basophilic cells were increased in numbers, and formed adenomatous nodules or diffuse masses beneath the pituitary capsule. In the diabetics with less than 4.5 per cent Type II thyroid cells, the basophils were predominantly rich in granules, with or without larger cytoplasmic vacuoles. These cells corresponded to the so-called normal basophils.

DISCUSSION

One advantage of the thyroid cell mapping method consists in the possibility of uncovering morphologic thyroid abnormalities not observed by ordinary pathological examination. Application of thyroid mapping to 42 cases of human diabetes mellitus has revealed evidence of an increased reabsorption of follicular colloid and its inferred secretion into the milieu interne, presumably as thyroid hormone. This stimulation of secretion averaged ten times that found in control thyroid glands in states of ordinary activity, as measured by the percentage of Type II columnar cells. The mean overactivity so measured was about one-fifth of the average found by cell counts in clinical hyperthyroidism. As is known clinically, some diabetics may have thyroid hyperactivity verging on thyrotoxicosis.[1]

Investigation of the basis of the thyroid stimulation pointed to elevations of the blood sugar level as responsible for some increases in percentages of Type II cells, as shown by the study of nondiabetics treated with intravenous glucose solutions shortly antemortem, as well as diabetics. Based on rather limited numbers of observations, absorption into the human adult's blood stream of about 100 gm. of glucose within 10 hours or 50 gm. within 5 hours appeared necessary to produce and maintain the histophysiologic response of increased Type II thyroid cells. It is planned to investigate this point further with animal experiments, taking into account the factors of body weight and rate of injection.

The percentage levels reached by Type II thyroid cells stimulated by increased blood concentrations of glucose did not appear to be regularly proportional to the degrees of hyperglycemia. That such changes were not seen after infusions of some patients in shock suggested that adequate circulation and hypothalamic-hypophyseal stimulation may be prerequisites for this thyroid activation. Theoretically this might be expected, from the present knowledge of the neurohormonal control of thyroid function.

In general, in adults it appears that hyperglycemia alone will not result in elevation of Type II thyroid cells above approximately 4.5 per cent, or ten times average normal numbers. If this be true, two-thirds of the human diabetic cases studied had thyroid stimulation attributable purely to their hyperglycemic states. The thyroid response was apparently histophysiologic, and no reactive or morphologic abnormality of the pituitary, adrenal, liver, or pancreas needed to be implicated, apart from their possible participation in producing hyperglycemia. Glucose metabolism would logically require that since the thyroid governs the metabolic rate, thyroid cells should also respond to changes in glucose concentration.

In the remaining third of the diabetics studied, there were over 5 per cent Type II thyroid cells found. Their pituitary glands contained nodular or diffuse anterior lobe masses of sparsely granulated basophilic cells, which were not observed in the pituitary glands of diabetics

with fewer Type II thyroid cells. The sparsely granulated basophils are thought to be analogous to the thyrotropic basophilic pituitary cells of rats,[6] and are known to undergo hyperplastic changes in various clinical and experimental thyroid abnormalities, including hyperthyroidism.[7] It is thought that in these diabetics excess thyrotropic hormone was being secreted, representing a pathologic pituitary alteration comparable to but less marked than that associated with hyperthyroidism.

It is apparent that the number of cases mapped and counted so far is insufficient for statistical study. Perhaps if 100 diabetic thyroids were mapped, the over-all incidences of Type II cells might show different distributions. However, the collection and study of large numbers of suitable cases are difficult, even in a laboratory closely associated with a large diabetic service like the Joslin Clinic. Further investigations of thyroid stimulation in human diabetes mellitus are planned, in particular to determine whether there is a mathematical correlation between the percentages of certain pituitary cells, particularly the sparsely granulated basophils, and Type II cell percentages as determined by thyroid mapping.

SUMMARY

Thyroid mapping and cell counts from 42 diabetic patients and controls revealed that a significantly increased activity of colloid resorption and an inferred increased thyroid hormone secretion were characteristic of human diabetes mellitus. Similar investigations of nondiabetics receiving intravenous glucose solutions shortly antemortem showed that hyperglycemia stimulated an increased colloid resorption. Hyperglycemia was considered responsible for the thyroid stimulation observed in two-thirds of the diabetic cases studied. In the diabetics with the most active colloid resorption, analogous to but less marked than that found in hyperthyroidism, the stimulation was ascribed to an abnormal pituitary hyperactivity, associated with increased numbers of sparsely granulated basophilic pituitary cells.

ACKNOWLEDGMENT

We are indebted to Dr. F. Thomas, Ghent, Belgium, for permitting the copying of Lefèvre's drawing, Plate 14, from his article,[4] and to Lois B. May for reviewing the clinical records.

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ABSTRACTS

Arteta, J. L.; König, C.; and Carballido, A. (*Institute of Experimental Endocrinology, Madrid, Spain*): THE EFFECTS OF GLUCOSE AND INSULIN ON THE DIABETOGENIC ACTION OF ALLOXAN. J. Endocrinol. (Brit.) *10*: 342-46, June 1954.

The previous injection of glucose, causing a transitory hyperglycemia, has a protective effect against the normally produced diabetes provoked by the rapid intravenous injection of alloxan. The authors do not consider this effect to be due to the hypertonicity of the injected solution because the injection of a hypertonic solution of sodium chloride eight minutes before the administration of alloxan did not have any permanent effect upon the glucose level of the treated dogs. On the other hand, the lowering of the level of blood glucose by means of adequate quantities of insulin sensitized the animals in such a way that even normally ineffective doses of alloxan induced definite diabetes.

Baird, Ian McLean; and Munro, Donald S. (*Royal Infirmary, Sheffield, England*): ADDISON'S DISEASE WITH DIABETES MELLITUS: A CASE TREATED WITH CORTISONE. Lancet *1*:962-64, May 8, 1954.

A cause of coexistent diabetes mellitus and Addison's disease is described. As the Addison's disease developed, the insulin requirements decreased. Cortisone therapy initially precipitated diabetic ketosis, but later a more cautious introduction of cortisone was successful. Clinical improvement ensued, although insulin requirements increased abruptly. A tendency to develop frequent hypoglycemic attacks was eliminated.

Becker, Bernard; Allen, Ruth; Winter, Frank C.; Maengwyn-Davies, Gertrude; Friedenwald, Jonas S. (*Wilmer Ophthalmological Inst., Johns Hopkins Hosp., Baltimore, Md.*): THE ROLE OF THE ADRENAL CORTEX AND VITAMIN B_{12} IN DIABETIC RETINOPATHY. Am. J. Ophth. *38*:53-59, July 1954.

Evidence has been reviewed for implicating excessive adrenal cortical function and vitamin B_{12} deficiency in the pathogenesis of diabetic retinopathy and the Kimmelstiel-Wilson lesion. The vitamin B_{12} test-dose excretion provides a useful clinical test for the presence or absence of retinopathy in the diabetic. The incidence of cortisone-induced renal lesions in rabbits is markedly increased by omission from the diet of supplementary vitamin B_{12} and aureomycin.

Bergsma, Daniel (*Trenton*): DIABETES, A PUBLIC HEALTH PROBLEM. J. M. Soc. New Jersey *51*:271-72, June 1954.

Case-finding of either diabetics or persons with tuberculosis is a prohibitively expensive process unless it is done on such a large scale that the unit cost is reduced to a minimum. This is obviously impractical for the average physician. It becomes an area in which the public health agency supplements the efforts of the practitioner. If proper procedures are used on large numbers of persons, even when those persons are presumably well, there will be found a number of reactors. The reaction is not a diagnosis. It is not the function of the public health agency to diagnose. The reaction or suspicion is merely a lead which enables us to refer the individual in question to a physician earlier than otherwise. The private practitioner makes the diagnosis, and determines the course of treatment. This effort is also an example of sound public relations. In the long run, an organization is judged not by what it says about itself but by what it does. To organize the search for unknown diabetics, you are proving that you are your brother's keeper and that you are interested in lifting the level of health in your respective communities.

Bertram, Ferdinand; Feldkirchner, Elisabeth; and Meinecke, Rolf (*Medizinischen Klinik des Allgemeinen Krankenhauses, Hamburg-Langenhorn*): NEW POSSIBILITIES OF AN OPTIMAL INSULIN THERAPY. Deutsche med. Wchnschr. *79*:28-31, January 1, 1954.

Lente Insulin NOVO, Insulin NPH 50 Lilly, and Long Insulin, Hoechst, represent a considerable advance toward an optimal insulin therapy. In about 70 to 80 per cent of moderately severe and severe cases of diabetes, higher insulin doses can be given unhesitatingly in one morning injection. Long Insulin as well as the other new depot insulins fail when the diet and the accustomed muscle work are not maintained. For this reason their use in juvenile diabetes frequently encounters difficulties. These insulins also fail in infections that cause an insulin resistance and in some cases of chronic infections, such as for example tuberculosis. When the metabolism is

disrupted under Long Insulin it is necessary temporarily to change to mixed insulin and then later to adjust the patients again to Long Insulin. Long Insulin is among the best depot insulins. The good subjective well-being of the patients must be particularly emphasized.

Boulin, R.; and Nepveux, F. (*Paris, France*): ZINC INSULINS WITH SLOW ACTION. Presse méd. *62*:1053-54, July 10, 1954.

Of the three types of insulin worked out by Hallasmøller, the most valuable seems to be lente insulin made from a mixture of amorphous insulin and crystalline insulin and having at least a 24-hour duration of action. The action of lente insulin is more advantageous than that of protamine zinc insulin because the oscillations in blood glucose present an amplitude a little less marked, although more marked than the physiological amplitude in normal subjects.

Cairns, A. and Constantinides, P. (*Dept. of Anatomy, University of British Columbia, Vancouver, Canada*): MAST CELLS IN HUMAN ATHEROSCLEROSIS. Science *120*:31-32, July ?, 1954.

The authors report further study upon a previously cited observation indicating an inverse correlation between tissue mast cell content and atherosclerosis. Mast cells were counted in toluidine blue-stained sections of myocardium from groups evenly divided between males and females: of 46 adults, 20 to 35 years old, without evidence of atherosclerosis; 48 adults, 60 to 90 years old, with marked generalized atherosclerosis; and 48 adults, 60 to 90 years old, without gross evidence of atherosclerosis. The values for the three groups were 297, 198, and 273, respectively. Among the nonatherosclerotic young adults, males had a lower count than females (239 to 351); atherosclerotic senile females had lower counts than nonatherosclerotic senile females (193 to 276); and there was no significant difference between the counts of nonatherosclerotic seniles and nonatherosclerotic young adults (273 to 297).

Caldwell, Renwick K. (*Medical Section, V. A. Hospital, Northampton, Mass.*): DIABETES MELLITUS FOLLOWING ACUTE PANCREATIC NECROSIS: REPORT OF A CASE. New England J. Med. *251*:228-30, August 5, 1954.

A case of acute pancreatic necrosis producing diabetes mellitus is presented. Acute pancreatitis and pancreatic necrosis should be considered as possible etiologic factors in diabetic acidosis, especially in the presence of abdominal pain.

Covington, J. M. (*Wadesboro, N.C.*): WHY WOMEN OUTLIVE MEN. J.A.M.A. *155*:707, June 12, 1954.

Males are less resistant to disease than females and this is true from birth onward. Nearly all diseases and defects cause more death among males than females. Exceptions are cancer, diabetes, exophthalmic goiter, and gallstones.

De Castro, Ary; and Teixeira, Walter (*University of Brasil Sch. of Med.*): DIABETES AND INFECTION. Med. cir. farm. *No. 218*:248-66, June 1954.

Three cases of diabetes complicated with infections are presented. The author emphasizes the importance of the use of chemotherapy and antibiotic therapy in the treatment of complicated diabetes. A diet containing a more liberal amount of carbohydrate and less fat is proposed.

Demis, Dermot J. and Rothstein, Aser (*Div. of Pharmacology, Dept. of Radiation Biology, University of Rochester Sch. of Med. and Dentistry, Rochester, N.Y.*): ABSENCE OF AN INSULIN EFFECT ON SUGAR UPTAKE BY RAT DIAPHRAGM UNDER ANAEROBIC CONDITIONS. Am. J. Physiol. *178*:82-84, July 1954.

The authors report that the rates of uptake of glucose, fructose, and galactose by excised rat diaphragm are the same under aerobic and anaerobic conditions. Insulin stimulates the uptake of each of the three monosaccharides under aerobic conditions but has no influence under anaerobic conditions. Anaerobiosis does not permanently destroy the ability of the diaphragm cell to respond to insulin. This action of insulin apparently depends on the presence of a cellular constituent which is present in adequate amounts only under aerobic conditions.

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dePeyster, F. A.; and Gilchrist, R. K. (*Presbyterian Hosp. of Chicago, Chicago, Ill.*): CLINICAL RESPONSE OF SPONTANEOUS HYPOGLYCEMIA TO DIETARY AND

DRUG THERAPY. J.A.M.A. *155*:884-89, July 3, 1954.

Medical management of spontaneous hypoglycemia is important in the period which precedes an operation. In three cases of spontaneous hypoglycemia ultimately treated by surgery, some remission of symptoms followed dietary, alloxan, corticotropin (ACTH) and cortisone therapy. A high protein, variable fat, and low carbohydrate diet, served in three meals with complementary feedings providing nourishment every three hours, is the most expedient management that may control hypoglycemic symptoms. The use of alloxan intravenously (150 to 250 mg. per kg.) proved totally ineffective in controlling hypoglycemic convulsions; corticotropin 25 to 75 mg., controlled hypoglycemic convulsions, cortisone, 50 mg., alone or in combination with corticotropin failed to prevent symptoms. Surgical excision of the islet cell adenoma remains the treatment of choice in spontaneous hypoglycemia of pancreatic origin.

Dituri, Bessie (*Temple Univ. Hosp., Philadelphia, Pa.*): INSULIN-RESISTANT DIABETES AFTER TOTAL PANCREATECTOMY. New England J. Med. *251*:13-16, July 1, 1954.

Resistance to insulin is reported in the case of a patient who had diabetes mellitus following total pancreatectomy. The presence of antibodies to insulin in the patient's serum was described. This case is compared with others who survived total pancreatectomy for more than a month. The problem of insulin resistance is briefly reviewed.

Dreiling, David A.; Richman, Alexander; and Klein, Alice (*Mount Sinai Hosp., New York, N. Y.*): EVALUATION OF PROVOCATIVE BLOOD ENZYME TESTS EMPLOYED IN DIAGNOSIS OF PANCREATIC DISEASE. A.M.A. Arch. Int. Med. *94*:197-212, August 1954.

The literature of the so-called provocative serum enzyme tests suggested for diagnosis in pancreatic disease is reviewed and assessed. An experimental study is presented of the blood amylase responses to morphine, secretin, methacholine (Mecholyl), and bethanechol chloride (Urecholine), singly and in combination, in 192 patients with and without proved pancreatic disease. An analysis of the results of this investigation leads to the conclusion that these serum enzyme response tests have no value in the diagnosis of pancreatic disorders.

Editorial: GLUCAGON. Nutrition Rev. *12*:132-34, May 1954.

It is generally recognized that glucagon is a protein factor extractable from the pancreas and isolated in crystalline form, which raises blood glucose presumably by stimulating hepatic glycogenolysis and increasing the activity of phosphorylase. When given intravenously (Kirtley, and others) to normal and stable diabetic subjects, the blood glucose continues to rise until the infusion is stopped when the glucose then falls below the initial level in 30 to 60 minutes. Serum inorganic phosphate level drops while the blood glucose rises, but pyruvate falls. Unstable diabetics failed to show a rise in blood glucose although a striking increase occurs after epinephrine.

It seems this substance is more a modifier of diabetes than a causative agent.

Editorials and Comments: TREATMENT OF PANCREATITIS ALONG WITH DIABETES. J.A.M.A. *155*:1240-41, July 31, 1954.

Pancreatitis can produce temporary hyperglycemia and glycosuria by interfering with islet cell function, a process that is sometimes reversible as the pancreatitis subsides. In rare cases, pancreatitis also causes permanent diabetes mellitus either by producing sufficient permanent islet cell damage or by precipitating clinical evidence of the disease in the person hereditarily predisposed to it. The treatment of pancreatitis in the diabetic would be the same as in the patient without diabetes. The presence of uncontrolled diabetes, especially with the acute type of pancreatitis, requires additional insulin. Actual coma has been caused by severe acute pancreatitis; at times resistance to insulin is marked, and requires intensive insulin therapy.

Eiduson, S.; Kingsley, G. R.; Portis, R. B.; and Wallace, R. D. (*Biochemistry Lab., Genl. Med. & Surg. and Neuropsychiatric Hosps. V. A. Center, & Dept. of Physiol. Chem. Sch. of Med., Univ. of California, Los Angeles*): EFFECT OF ELECTROSHOCK THERAPY ON BLOOD LACTIC ACID AND PYRUVIC ACID. Proc. Soc. Exper. Biol. & Med. *84*:364-67, November 1953.

A simultaneous measurement has been made of lactic acid and pyruvic acid changes in the blood of neuropsychiatric patients before and after extreme muscular excitation induced by electroshock therapy (EST). The

blood lactic acid level of all patients following EST rose sharply to a peak (six times preshock level) within 3 to 5 minutes and then returned to the normal level after 1 to 1½ hours. The blood pyruvic acid level of all patients rose immediately following EST for thirty seconds (4 to 6 mg. per cent), then fell to a minimum (2 to 3 mg. per cent) within 3 to 5 minutes and rose again to a peak three times the preshock level 20 minutes after EST.

Ellis, Sydney; Anderson, Hilton L.; and Collins, Margaret C. (*Dept. of Pharmacol. and Pathol., Temple Univ. Sch. of Med., Philadelphia, Pa.*): PHARMACOLOGIC DIFFERENTIATION BETWEEN EPINEPHRINE- AND HGF-HYPERGLYCEMIAS: APPLICATION IN ANALYSIS OF COBALT-HYPERGLYCEMIA. Proc. Soc. Exper. Biol. & Med. *84*:383-86, November 1953.

Dihydroergotamine (DHE) did not interfere with the glycogenolytic effect of the hyperglycemic-glycogenolytic factor (HGF) on rabbit liver slices or on hyperglycemia in intact rabbits. Comparable effects of epinephrine in vitro or in vivo were antagonized by DHE. The hyperglycemia induced by cobaltous chloride, which destroys alpha cells of the pancreatic islets, was prevented by DHE.

This hyperglycemia is attributable to sympathetic nerve stimulation. No evidence for the release of HGF was obtained. Blood sugar was maintained at a normal level in rabbits pretreated with cobalt, then fasted and injected with DHE to limit sympathetic action on the liver.

Fasoli, Angelo; Glassman, Morton D.; Magid, Edward B.; and Foa, Piero P. (*Dept. of Physiol. and Pharmacol., Chicago Med. Sch., Chicago, Ill.*): SERUM LIPOPROTEINS IN EXPERIMENTAL DIABETES. II. ACTION OF HEPARIN IN VIVO ON LIPOPROTEINS OF DEPANCREATIZED DOGS. Proc. Soc. Exper. Biol. & Med. *86*:298, June 1954.

Heparin causes a clearing of the lipemic serum of normal dogs; it has this effect to a lesser extent in depancreatized dogs.

In normal animals with alimentary hyperlipemia, this clearing is associated with a decrease in the lipid content of the slow-moving lipoprotein fractions. However, in the diabetic lipemic dogs, the outstanding change is the appearance of, or sharp increase in, the amount of a fraction migrating faster than albumin and containing large quantities of lipids.

Ferner, Helmut (*Hamburg, Germany*): THE *a*- AND β-CELLS OF THE PANCREATIC ISLETS AS SOURCE OF THE ANTAGONISTIC HORMONES GLUCAGON AND INSULIN. THE SHIFT OF THE *a*-β-RELATION IN DIABETES MELLITUS. Am. J. Digest. Dis. 20:301-06, October 1953.

Recent observations indicate that two hormones, insulin and glucagon, are produced by the islet system of the pancreas. The beta cells produce insulin and the alpha cells, glucagon, which are antagonists.

The ratio or alpha to beta cells, and not the total volume of cells, is the important point in blood sugar control. Shifts in this ratio to a predominance of alpha cells are seen in diabetes.

Unlike the beta cells, the alpha cells are under the influence of a tropic hormone produced by the anterior pituitary lobe. This tropic substance is either identical with or closely related to the growth hormone.

Foreign Letters (*Denmark*): CAUSES OF DEATH AMONG DIABETICS. J.A.M.A. *155*:769, June 19, 1954.

The diabetic male dies at an earlier age than the diabetic female and diabetics of both sexes die younger than normal persons in the community. In such a study, it is difficult in many cases to decide the exact part played by diabetes itself as the principal cause of death. This Danish study shows that the combination of diabetes with cancer was much the same as that found by Joslin; in the former study 9.7 per cent of the deaths among diabetics was due to cancer and in the Joslin series, 8.8 per cent. One of the Danish tables lists the contributions made by renal disease, arteriosclerosis, diseases of the respiratory system, heart disease, and tuberculosis to deaths among diabetics.

Foreign Letters (*Chile*): RENAL CHANGES IN DIABETICS. J.A.M.A. *155*:664, June 12, 1954.

Clinical manifestations of diabetes and nephropathy are reported in 16 patients. As a control group, 15 patients with diabetes without renal complications were studied. In the control group the blood cholesterol level was normal, although in the other group it was always high. This abnormality might explain the presence of arteriosclerosis in the group with nephropathy. The practically constant fall in serum albumin in patients with diabetic nephropathy but not in diabetics without such a complication might suggest that the renal changes are intimately associated with changes in the proteinemia.

Gelfand, Maxwell L.; Fabrykant, Maximilian; and Ashe, Benjamin I. (*Dept. of Med., New York Univ. Postgraduate Med. Sch., & Bellevue Hosp., N. Y.*): SENSITIVITY TESTS TO INSULIN IN PATIENTS WITH LOCAL SKIN LESIONS FROM INSULIN. Proc. Soc. Exper. Biol. & Med. 86:258-61, June 1954.

Sixteen diabetic patients exhibiting local skin reactions to insulin as nodules with or without erythema or stinging were tested intradermally with various insulin products, beef and pork protein. Sixteen nondiabetics not using insulin were similarly tested with the same substances. Passive transfer tests with the sera of five patients manifesting local reactions to insulin were performed. Skin reactions noted in patients exhibiting local reactions to insulin were no different from those obtained in the control group of nondiabetics, nonusers of insulin. The Prausnitz-Kustner passive transfer phenomenon was absent in all five instances. The authors conclude that local nodules with or without stinging or erythema observed in patients receiving insulin therapy are not due to any antigen-antibody mechanism.

Goetz, Frederick; Beigelman, Paul M.; and Thorn, George W. (*Dept. of Med., Harvard Med. School, and the Medical Service, Peter Bent Brigham Hosp., Boston, Mass.*): A METHOD OF INSULIN BIO-ASSAY AND ITS APPLICATION TO PLASMA FRACTIONS. Proc. Soc. Exper. Biol. & Med., 86:484-86, July 1954.

Minute quantities of insulin were assayed using hypophysectomized-alloxanized mice. The method of Anderson was modified in that the diminution in the increment of blood sugar 65 minutes after dextrin gavage compared to controls was used. Various plasma fractions were tested, and a globulin-rich fraction precipitated by zinc was found to show insulin-like activity by this technic.

Gofman, John W.; Glazier, Frank; Tamplin, Arthur; Strisower, Beverly and De Lalla, Oliver (*Donner Lab., Div. of Med. Physics, Dept. of Physics, and the Radiation Lab., Univ. of Calif., Berkeley, Calif.*): LIPOPROTEINS, CORONARY HEART DISEASE, AND ATHEROSCLEROSIS. Physiol. Rev. 34:589-607, July 1954.

The authors review the evidence implicating certain classes of human serum lipoproteins in coronary heart disease and coronary artery atherosclerosis and point out the independent etiologic significance of diastolic hypertension. Based upon information from lipoprotein and diastolic blood pressure findings, the authors have calculated a composite function, designated alpha-function, which is utilized in estimating relative risks of developing human coronary heart disease. The integrated exposure to alpha-function levels over progressive years in duration provides predictive information concerning coronary heart disease in reasonable accord with actuarial experience.

Goldner, Martin G.; Brown, Raymond A.; Cohen, Clifford; Cox, Herold; Lasser, Richard P. (*Jewish Sanitarium and Hosp. for Chronic Diseases, Brooklyn; The Jacques Loewe Research Foundation Labs.; The Jewish Hosp. of Brooklyn; and the Viral and Rickettsial Res. Labs., Lederle Labs. Divs. American Cyanamid Company, Pearl River, N.Y.*): SERUM LIPOPROTEIN PATTERNS IN A GROUP OF ELDERLY DIABETICS. Am. J. M. Sc. 227:618-23, June 1954.

Serum lipoprotein determinations have been performed in a series of 41 elderly diabetics with a variety of clinical syndromes. It was observed that patients with peripheral vascular disease showed higher levels in the Class S_f 35-100 than were found in those with cerebrovascular disease alone or in those without peripheral vascular, cardiovascular or cerebrovascular disease. This relationship was shown to be statistically significant. The groups were shown not to be significantly different with respect to age, sex, duration or severity of diabetes, presence of renal disease or hypertension. Cream ingestion was found to affect the serum lipoprotein patterns of these individuals, establishing the importance of obtaining specimens in the fasting state.

Goldner, Martin G., and Jauregui, Raul Hernandez (*Dept. of Med., Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, N. Y.*): HYPOGLYCEMIC ACTION OF AN ANTIHISTAMINIC: A CLINICAL EVALUATION. Am. J. Digest. Dis. 21:160-63, June 1954.

Various antihistamines have been described as having a lowering effect on the blood sugar. The therapeutic value of the hypoglycemic action of various antihistaminic drugs certainly would be limited for several reasons. Their action is only slight and the rather low potency of such drugs would be useful in the very mild diabetic state and perhaps in some of the patients who require two doses of insulin, one of these might possibly be substituted for the second dose. The antihistaminic anta-

zoline hydrochloride has a rather moderate hypoglycemic action and the mechanism and therapeutic value are discussed.

Goldring, William and others. (Panel Discussion) (*The New York Academy of Med., New York, N. Y.*): HYPERTENSIVE VASCULAR DISEASE. Bull. New York Acad. Med. 30:376-98, May 1954.

The incidence of arteriosclerosis in hypertensives just as in diabetics, is far higher than in the control population. However, most of the evidence points to arteriosclerosis and hypertension pursuing independent courses, although either may aggravate the other.

The interest in sympathectomy was reported to be on the wane in view of the newer drugs which are said to perform "a medical sympathectomy."

González Villasante, J.; and Jiménez Díaz, C. (*Dept. of Experimental Med., Univ. of Madrid*): EFFECTS OF NEPHRECTOMY, PANCREATECTOMY AND ALLOXAN POISONING ON GLUCOSE UTILISATION BY THE MUSCLE "IN VITRO" (STUDIES ON THE DIAPHRAGM OF RAT). Bulletin of the Institute for Medical Research, University of Madrid 4:113-24, July-September 1951.

The modifications in glucose utilization by the diaphragm of rats in various conditions are studied. It may be seen that addition of insulin increases utilization. This effect is more marked in rats suffering from alloxan or post-pancreatectomy diabetes.

Goodman, Joseph I. (*Western Reserve Univ., Mt. Sinai Hosp., Highland View Hosp., and Cuyahoga County Nursing Home, Cleveland, Ohio*): COMPLICATIONS OF DIABETES IN OLDER PATIENTS. J. Am. Geriat. Soc. 2:351-58, June 1954.

The complications of diabetes mellitus reviewed in this paper are *complications* in the truest sense of the word. Conditions such as acidosis, retinopathy, glomerulosclerosis, neuropathy and hepatomegaly, which are considered by many as inherent to diabetes, are classed as components and not considered here. The most significant complications found in elderly diabetic patients are atherosclerosis, ophthalmologic conditions, benign prostatic hypertrophy and chronic infections.

The generic concept of arteriosclerosis lacks specificity and is no longer acceptable. The types of vascular disease especially accelerated by diabetes are coronary atherosclerosis, gangrene, and renal arteriosclerosis. Atherosclerosis was detected in 96 per cent of 59 patients who were over 60 years of age at the onset of diabetes. The best clinical criteria for the early detection of atherosclerosis are reviewed briefly. The importance of prophylactic foot care is stressed in the prevention of gangrene.

Goodman, Joseph I. (*Cleveland Heights, Ohio*): PREVENTION OF INSULIN HYPOGLYCEMIA. Am. Pract. & Digest Treat. 5:464-67, June 1954.

The author discusses the seriousness of insulin reactions, citing instances in various stations in life. He believes that they are most commonly due to the long acting insulins. The author has stressed the importance of preventing rather than treating hypoglycemia. He presents a program of rearranging a diet schedule to provide anticipatory feedings just before the time of maximum insulin action for each preparation.

Gundersen, Kare; Bradley, Robert F.; and Marble, Alexander (*Baker Clin. Res. Lab., New England Deaconess Hosp., and the Joslin Clin., Boston, Mass.*): SERUM PHOSPHORUS AND POTASSIUM LEVELS AFTER INTRAVENOUS ADMINISTRATION OF GLUCOSE. THEIR USE AS DIAGNOSTIC AIDS IN DIABETIC AND NON-DIABETIC SUBJECTS WITHOUT LIVER DISEASE. New England J. Med. 250:547-54, April 1, 1954.

Eleven normal volunteers and 41 patients were studied by means of an intravenous glucose tolerance test, with concomitant determinations of serum inorganic phosphorus and serum potassium. An evaluation of liver function was made on the basis of history, physical findings, and a battery of liver function tests.

Twenty-four subjects had a normal glucose curve, and the maximum phosphorus fall averaged 19 per cent, with a wide range of 4 to 35 per cent. In the 4 with a borderline sugar tolerance test, the maximum decrease in phosphorus was 22 per cent, with a range of 13 to 29 per cent. The 24 diabetic subjects averaged a maximum phosphorus fall of 18 per cent, with a range of 5 to 35 per cent. There was thus no significant difference in the average maximum reduction in phosphorus, and the ranges of values overlapped greatly.

Of the 26 persons with no evidence of impaired liver function, 17 showed normal, 2 borderline, and 7 dia-

betic glucose tolerance; the maximum phosphorus fall averaged 19.8 per cent. Of 5 patients with definite liver disease, 4 were diabetic and 1 normal according to the intravenous glucose tolerance test; the maximum drop in phosphorus averaged 15.8 per cent. Among 21 subjects with questionable evidence of liver disease, the average phosphorus fall for the 6 with hepatomegaly and for the 15 with minimal abnormality in liver function tests were 16.1 and 19.4 per cent, respectively.

Decreases in serum potassium average 0.33 mEq/L. in the patients with normal glucose tolerance and 0.32 mEq. in those with diabetic curves. The ranges of values were almost identical. From these data slight degrees of insulin deficiency could not be distinguished. The maximum fall of phosphorus during an intravenous glucose tolerance test in patients with lesser degrees of decreased carbohydrate tolerance cannot safely be relied on to differentiate so-called hepatic storage insufficiency from true diabetes mellitus.

Patients with persistent hyperglycemia and glycosuria should be treated as diabetic. If liver disease is present, both conditions should be treated simultaneously.

Gurling, K. J.; Rackow, F.; and Smith, M.J.H. (*King's Coll. Hosp., London, England*): ADDISON'S DISEASE COMPLICATED BY PREGNANCY AND DIABETES MELLITUS. Lancet 2:316-18 August 14, 1954.

Hitherto in women with Addison's disease, not only has pregnancy been uncommon but subsequent management, even with desoxycortone acetate, has been difficult. The development of diabetes mellitus brought additional hazards, but treatment with cortisone and salt, with careful control of the diabetes, enabled the pregnancy to proceed normally. There is no reason why pregnancy should not be permitted in such a case, provided that full laboratory facilities are available, so that appropriate adjustments of the cortisone, salt, and insulin may be made.

Harrison, Mary T. (*Cleveland Clinic*): THE NURSE IN A DIABETIC CHILDREN'S CAMP. Nursing Outlook 2:292-93, June 1954.

Working in the camp provides a pleasant, relaxing change from the usual hospital or office routine. Here is a chance to get out of that white uniform! The nurses wear sports clothing, and don their whites only for the opening and closing days of camp. They have much free time in which to pursue their hobbies and favorite sports. The counselors are always happy to help with tennis problems, swimming instructions, and similar athletic coaching. But the greatest reward which accrues from this work lies in the very nature of the camp itself. It offers the nurse an unequalled opportunity to become familiar with the day-to-day problems of diabetic children. They usually lead rather regimented lives at home, and as a result, personality problems frequently arise. The nurse often plays the role of a "second mother" to these campers, sharing their problems and confidences, and, incidentally, learning a great deal about diabetes in children. Nurses and counselors who work at these camps for the first time invariably are quite impressed with the way in which the youngsters take diabetes in their stride. There is a tremendous group spirit; all of them share a common problem—a handicapping disease. They all benefit from associating with others like themselves so that, in reality, the camp experience is a type of group therapy.

Hartmann, Alexis F.; McCoy, Ernest E.; Swarm, Pauline A.; and Nakasato, Doris I. (*Dept. of Pediat., Washington Univ. Sch. of Med., St. Louis Children's Hosp. and St. Louis Maternity Hosp., St. Louis, Mo.*): FURTHER OBSERVATIONS ON THE METABOLISM OF GALACTOSE IN INFANTS AND CHILDREN. J. Pediat. 44:499-507, May 1954.

Both full-term and premature infants, if otherwise normal, can metabolize galactose normally at birth. Protracted withdrawal of lactose from the diet of a normal child does not lead even temporarily to deficiency in metabolizing galactose. Some premature infants, failing to do well, may be found to have severe hypoglucemia, masked by galactosemia, and resemble the young infants with diarrhea previously reported. The metabolic defect seems linked with malnutrition and, possibly, immaturity of development. Galactosuria occurs regardless of blood concentration, but increases with rising blood values. When extreme, there may be associated glucosuria, despite normal or even low blood glucose concentrations.

Hartmann, Alexis F.; Wohltmann, Hulda J.; and Hartmann, Alexis F., Jr. (*Dept. of Pediat., Washington Univ. Sch. of Med., St. Louis, Mo.*): DIETARY FRUCTOSE IN CHILDREN WITH DIABETES MELLITUS. J. Pediat. 45:27-50, July 1954.

In order to determine whether fructose feeding would influence insulin requirement in diabetes mellitus, five children with severe diabetes were studied. Three interchangeable arrangements were used which caused the diet to vary from a standard one to (1) one which permitted fructose to furnish 25 per cent of the total calories, (2) sucrose to be substituted in equal amounts for fructose, and (3) glucose to be similarly substituted.

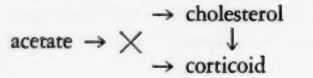
In four of the children, despite the varying diets, insulin dosage remained constant, and in them it was concluded that fructose exerted no insulin-sparing effect. In the fifth child, what at first seemed to be an insulin-sparing effect, was eventually interpreted as spontaneous improvement of tolerance often seen in the earlier stages of juvenile diabetes mellitus.

Hechter, Oscar; and Pincus, Gregory (*Worcester Foundation for Experimental Biology, Shrewsbury, Mass.*): GENESIS OF THE ADRENOCORTICAL SECRETION. Physiol. Rev. *34*:459-96, July 1954.

The authors summarize present knowledge concerning the biosynthesis of adrenal cortex steroids in three categories: (1) nature of the steroidal products released into the circulation (2) the precursors and metabolic pathways involved in the elaboration of these steroids, and (3) the role of corticotropin in corticosteroid biosynthesis.

Despite considerable variation among species and among individuals in a single species, either corticosterone and/or hydrocortisone comprises 54 to 77 per cent of the total corticosteroid output. The latter dominates in man. Among the residual "trace" corticosteroids is the "electrocortin" recently identified as aldosterone, the major adrenal cortical factor regulating electrolyte metabolism. In addition to the above-cited corticosteroids, all possessing an 11-beta hydroxy function, the adrenocortical secretion contains androgenic activity and trace amounts of at least three 17-ketosteroids. The range of magnitude of corticosteroid secretion is of the same order in all species, with maximal rates of 3600 micrograms/gm. gland/hr. Hypophysectomy reduces the output to one-fifth to one-tenth of normal in dogs.

In vitro and in vivo studies indicate acetate and cholesterol to be basic precursors of adrenocortoid secretion and point toward a dual synthetic pathway in which cholesterol is involved but not necessarily involved:



Heinsius, Ernst: THE TREATMENT OF DIABETIC RETINITIS. Arch. f. Ophth. *153*:459-70, 1953. Am. J. Ophth. *37*:300, February 1954.

The author presents various procedures which have been employed in cases of retinal arteriosclerosis, capillary damage and periphlebitis.

Holst, Johan: SOME PROBLEMS IN THE OPERATIVE TREATMENT OF HYPERINSULINISM. Act. chirurgica scandinavica *105*:138, 1953. Abstr. from Surg., Gynec., & Obst. *97*:562-63, December 1953.

In the treatment of hyperinsulinism the risk of overlooking a tumor, especially in the heel of the pancreas, is great. If an islet tumor is not found on inspection and palpation in a case of hyperinsulinism, transections should be done.

Houssay, B. A.; Rodriguez, R. R.; Cardeza, A. F. (*Instituto de Biologia y Medicina Experimental Buenos Aires*): PREVENTION OF EXPERIMENTAL DIABETES WITH ADRENAL STEROIDS. Endocrinology *54*:550-52, May 1954.

White rats of 80 to 100 gm. weight had the ovaries and 95 per cent of the pancreas removed, which resulted in a 77 per cent incidence of diabetes in 6 months in the control group.

(a) Desoxycorticosterone acetate in dosages of 100 *u*g. per day caused no increase in diabetic incidence nor change in endocrine gland size.

(b) Compounds A, E, and F in dosages of 50 *u*g. per day resulted in a diabetic incidence of only 11 to 37 per cent at the end of 6 months and the occurrence of a marked hypertrophy and hyperplasia of the islets of the pancreas without change in the weight of the endocrine glands in the animals not developing diabetes.

(c) Compound E in dosages of 150 *u*g. per day resulted in an initial increased incidence of diabetes to 58 per cent at 2 months and a secondary decreased incidence of diabetes to 35 per cent at 6 months.

Hurwitt, Elliot S.; Altman, Stanley F.; Gerst, George R.; and Webber, Banice M. (*Montefiore Hosp., New York, N.Y.*): GASTROINTESTINAL BLEEDING DUE TO SPLENIC VEIN OBSTRUCTION BY PANCREATIC TUMORS. A.M.A. Arch Surg. *68*:7-11, January 1954.

Three cases are presented of massive gastrointestinal

bleeding associated with splenic vein obstruction due to pancreatic tumors. Splenectomy and removal of the tumor obstructing the splenic vein resulted in complete cessation of gastrointestinal bleeding in all three instances. Carcinoma of the pancreas was found in two cases. Involvement of the tail of the pancreas by Hodgkins disease was responsible for the venous obstruction in the third case. In all cases of obstructive splenomegaly with gastric varices and gastrointestinal bleeding, a thorough search for a locally obstructing lesion must be made before performing a venous shunt operation, as for the relief of portal obstruction.

Ingle, Dwight J.; Beary, Dexter F.; and Purmalis, Andrejs (*Res. Lab., The Upjohn Co., Kalamazoo, Mich.*): EFFECT OF CONTINUOUS INJECTION OF GLUCAGON UPON GLYCOSURIA OF PARTIALLY DEPANCREATIZED RATS. Proc. Soc. Exper. Biol. & Med. *85*:432-33, March 1954.

The administration of a highly purified preparation of glucagon to partially depancreatized, force-fed rats by continuous *intravenous* injection resulted in a temporary exacerbation of the diabetes. The continuous *subcutaneous* injections of glucagon to normal and to partially depancreatized rats were ineffective in the doses (0.05 to 1 mg. per rat per day) tested.

Ingle, D. J.; Meeks, R. C.; and Beary, B. F. (*Res. Labs., The Upjohn Co., Kalamazoo, Mich.*): LEVEL OF LIVER GLYCOGEN IN RATS HAVING STEROID DIABETES. Proc. Soc. Exper. Biol. & Med. *84*:334-36, November 1953.

Normal male rats were force-fed a medium carbohydrate diet. Steroid diabetes was induced by the administration of cortisone acetate in doses of 2, 5, 10, and 20 mg. per rat per day for seven days. The level of liver glycogen reached very high values in both fed and fasted animals. The glycogen level was proportional to the dose of cortisone acetate and was correlated with the level of urinary glucose.

Inoue, M.: BIOCHEMICAL STUDY OF EXPERIMENTAL DIABETIC CATARACT CAUSED BY ALLOXAN AND DITHIZONE. SECOND REPORT. Acta Soc. Ophth. Japan *57*: 1008-17, September 1953. Abstr. from Am. J. Ophth. *37*:459, March 1954.

The author claims that the combined administration of vitamin E with vitamin B_2 and potassium chloride retards the development of cataract in rabbits with experimental diabetes caused by alloxan and dithizone and also reduces the already developed opacity of the lens.

Jauregui, Raul Hernandez; and Goldner, Martin G. (*Depts. of Med., Jewish Sanitarium and Hosp. for Chronic Diseases, & the State Univ. of N. Y., Med. Center at N. Y., Brooklyn, N. Y.*): EFFECT OF HISTAMINE, EPINEPHRINE AND ANTIHISTAMINE (ANTISTINE) ON GLUCOSE TURNOVER IN THE ISOLATED LIVER. Proc. Soc. Exper. Biol. & Med. *85*:347-49, February 1954.

The isolated liver of the bullfrog was perfused with oxygenated amphibian Ringer glucose solution. The glucose concentration of the perfusate returning from the liver was determined in control experiments and under the influence of histamine, antihistamine, (Antistine) and epinephrine. Histamine and epinephrine caused an increase of the glucose concentration, probably due to enhanced glycogenolysis. Antistine caused a retention of glucose in the hepatic tissue and inhibited the spontaneous hepatic glycogenolysis induced by histamine and epinephrine.

Johnson, Jerry (*Maxwell Air Force Base, Alabama*): CATARACTS IN GALACTOSEMIA. Am. J. Ophth. *36*:1380-86, October 1953.

Galactosemia, or galactose diabetes, in a rare congenital abnormality characterized by a derangement in the metabolism of galactose. Galactose and glucose are the monosaccharides resulting from the breakdown of lactose. The cause of this disorder is obscure but presumably it is due to some primary hepatic defect. The onset is in the first weeks of life.

The outstanding features of the syndrome are as follows: cataracts, hepatomegaly, splenomegaly, failure to gain weight, and reducing substance in the urine. Frequently associated phenomena are persistent icterus, anemia, lethargy, absence of deep reflexes, mental retardation, and a familial tendency. The diagnosis may be definitely established by isolation of the phenylosazone of galactose from the urine.

It would be well for all ophthalmologists, when examining an infant with cataracts of uncertain etiology, to insist that an examination of the urine for reducing substances be performed in order that this rare syndrome may not be overlooked. Treatment, by removing milk

from the diet, before the third month of life, is stressed in order to prevent irreversible lens opacification.

Kadota, Ichiro; and Tokuyoshi, Abe (*Dept. of Path., Kyoto Univ. Sch. of Med., Kyoto, Japan*): CHEMICAL SPECIFICITY OF DIABETOGENIC ACTION OF QUINOLINE DERIVATIVES. J. Lab. & Clin. Med. *43*:375-85, March 1954.

The diabetogenic action of thirteen quinoline derivatives structurally related to 8-hydroxyquinoline was examined in rabbits. Close correlation between chemical structure and diabetogenic action in quinoline compounds was established; 8-hydroxyquinaldine and 5-amino-8-hydroxyquinoline were confirmed to be diabetic, but 8-methoxyquinaldine was not. An hydroxy group in position of 8 of quinoline was essential for diabetogenic action. The addition of hydroxy and carboxyl groups abolished the specific effect and this was also associated with a decrease in toxicity. Since diabetogenic 8-hydroxyquinaldine and 5-amino-8-hydroxyquinoline have properties of an organic agent which reacts with various metals, a close correlation between destructive action of the pancreatic islet cells and binding properties with metal ions (such as zinc) was confirmed.

Kaye, Ruth K. (*Camp NYDA, Burlingham, N. Y.*): SUMMER CAMP FOR DIABETIC CHILDREN. Am. J. Nursing *54*:972-74, August 1954.

The author discusses her experience at a summer camp for diabetic children, the camp schedule and routine, and the inestimable values of such an experience to diabetic children, as well as to those interested in the care and problems of diabetic children.

Keiding, Nils Rud (*Baker Clin. Res. Lab., New England Deaconess Hosp., Boston, Mass.*): LEVELS OF SERUM PROTEIN FRACTIONS IN DIABETIC PATIENTS WITH *Retinitis Proliferans*. Proc. Soc. Exper. Biol. & Med. *86*:390-94, June 1954.

The serum protein-bound carbohydrates and the serum protein fractions were studied in diabetic patients with retinitis proliferans. The serum protein-bound carbohydrates were found to be present in a higher concentration than in nondiabetics. By the method of paper electrophoresis, a definite decrease in the values for the albumin $+a_1$-globulin fraction and an increase in the a_2-globulin fraction was also found in all of the diabetics, although only those with both retinitis proliferans and proteinuria showed a decrease in the total protein. In the β-globulins no essential change was seen. In the group showing both retinitis proliferans and nephropathy the γ-globulin concentration tended to be lower than in the group with retinitis proliferans alone, but none of the groups had values distinctly different from those of nondiabetics. It is concluded that disturbances in the protein pattern exist which particularly involve the albumin and a_2-globulin fractions at a stage in the development of the diabetic vascular lesions where the changes cannot be accounted for by loss of protein in the urine.

Keitel, H. G.; and Keitel, N. B. (*Bethesda, Md.*): RAPID SIMPLE METHOD FOR DETERMINATION OF SERUM POTASSIUM. J.A.M.A. *153*:799-800, October 31, 1953.

A micromodification of the cobalt nitrite method for the determination of serum potassium content is described. With the use of equipment available in the simplest laboratory, the serum potassium concentration can be estimated in a few minutes.

Klatskin, Gerald (*Dept. of Internal Med., Yale Univ. Sch. of Med.*): THE ROLE OF ALCOHOL IN THE PATHOGENESIS OF CIRRHOSIS. Yale J. Biol. & Med. *26*:23-37, September 1953.

Animals given a high-protein diet showed none of the ill effects of prolonged ingestion of alcohol exhibited by animals subsisting on a low-protein diet.

A review of the evidence reveals that while dietary factors play an important role in the pathogenesis of alcoholic cirrhosis, a great deal remains to be learned about the complex interrelationships between alcohol consumption, dietary deficiencies, and alterations in the structure of the liver.

Kritchevsky, D.; Moyer, A. W.; Tesar, W. C.; Logan, J. B.; Brown, R. A.; Davies, M. C.; and Cox, H. R. (*Viral and Rickettsial Res. Sect., Lederle Labs. Div., American Cyanamid Company, Pearl River, N. Y.*): EFFECT OF CHOLESTEROL VEHICLE IN EXPERIMENTAL ATHEROSCLEROSIS. Am. J. Physiol. *178*:30-32, July 1954.

Rabbits were maintained on normal rabbit food augmented with 3 per cent cholesterol in corn oil, 3 per cent

cholesterol in a partially hydrogenated vegetable fat (commercial shortening) and 3 per cent cholesterol, respectively, for two months. The animals were then killed and their aortas graded visually for atheromatous lesions. The average severity of the lesions was 2.71 for the cholesterol-corn oil group, 3.71 for the cholesterol-shortening group and 3.80 for the cholesterol group. The data indicates the cholesterol vehicle plays a significant role in atherogenesis induced by cholesterol feeding.

Lamphier, Timothy A.; Wickman, William; Long, N. Gillmor (*Boston, Mass.*): CYSTOGASTROSTOMY FOR PANCREATIC CYST. REPORT OF A CASE. A.M.A. Arch. Surg. 68:666-76, May 1954.

Surgical intervention is indicated in every case of suspected or proved pancreatic cyst. Conservative therapy, because of the untoward sequelae, has proved to be unsatisfactory. Conservative therapy is also contraindicated because of the possibility of carcinomatous degeneration of a cyst, and because of the possibility of rupture of the cyst into the peritoneal cavity, with an attendant mortality of 60 per cent. Pancreatectomy is the best treatment, whenever possible. Simple drainage by means of a large rubber catheter, a cigarette drain, or marsupialization may be used in those cases unsuitable for excision. There are many disadvantages of such management, such as the persistence of draining fistulas, the excoriation effect of pancreatic juice on the skin, and the tendency to recurrence. The method of internal drainage, used in the case reported, will obviate the disagreeable features of external drainage, and will insure adequate drainage. It has been shown roentgenologically at various time intervals following pancreatic cystogastrostomy that abnormalities of the stomach at the site of the anastamosis fail to exist, and that eventually the cystic cavity atrophies and disappears. Another case report of successful pancreatic cystogastrostomy is added to the literature.

Lancaster, H. O. (*Sch. of Public Health and Tropical Med., Sydney*): THE MORTALITY IN AUSTRALIA FROM CANCER OF THE PANCREAS. M. J. Australia 1:596-97, April 17, 1954.

It might be expected that any chronic disease such as cancer affecting the pancreas would lead to dysfunction and sometimes to diabetes. This expectation appears to be borne out by figures from the review of cancer in London of Harnett (1952); 4 per cent of 245 patients with cancer of the pancreas had coexisting diabetes. This rate is much higher than in cancer of other sites; 1.2 per cent of 395 patients with recto-sigmoid cancer had coexisting diabetes, 0.6 per cent of 928 patients with cancer of the rectal ampulla, 0.6 per cent of 1430 patients with cancer of the stomach, none of 473 patients with cancer of the esophagus, 1.1 per cent of 2129 patients with cancer of the breast, and 0.8 per cent of 383 patients with cancer of the prostate. Harnett's (1952) report is, therefore, good evidence that patients with cancer of the pancreas are more prone to develop diabetes than are other cancer patients.

In contrast to the concentration on whether patients with cancer of the pancreas develop diabetes, we may equally well inquire whether diabetics develop cancer of the pancreas. The number of cases of cancer to be expected during one year in a given number of persons aged, say, sixty to sixty-four years, may be estimated. The author has computed the expected numbers of cancer of the pancreas by provisionally assuming that there is no association between cancer and diabetes, and that the expected number is the sum of the products, mortality rate by years experienced, taken for every age group. There are many more patients with cancer of the pancreas than were expected—four males instead of an expected number of fewer than one, and eight females instead of one. For males, there were fewer deaths from cancer of other sites than was to be expected, whereas for females there were rather more.

Lang, Stanley; Goldstein, M. S.; Levine, Rachmiel (*Dept. of Metabolic and Endocrine Research. Med. Res. Inst. Michael Reese Hosp. and the Dept. of Physiology, Univ. of Chicago, Chicago, Ill.*): INFLUENCE OF THE LIVER ON UPTAKE OF GLUCOSE BY EXTRAHEPATIC TISSUES. Am. J. Physiol. 177:477-50, June 1954.

The maximal glucose utilization exhibited by the peripheral tissues in the hind legs of the eviscerated dog is approximately 600 mg. per kg. per hr. By contrast, these same tissues in the intact animal can take in as much as 1500 mg. per kg. per hr. of glucose. This difference in carbohydrate utilization is independent of insulin since the presence of supermaximal amounts of insulin (10 units per kg. per hr.) cannot restore this utilization defect to the eviscerated animal; while high blood glucose levels alone can promote high uptake of sugar in the insulin-free depancreatized animal. The high

glucose uptake of the peripheral tissues appears to be dependent upon the release of some 'humoral' agent or influence by the liver in the presence of a carbohydrate load and can be demonstrated by cross transfusion. The liver would appear, therefore, to promote the peripheral storage and transformation of excess carbohydrate rather than serve itself as a major depot.

Langley, L. L.; Scokel, P. W.; Moore, E. J. (*Med. Coll. of Alabama, U. of Alabama School of Dentistry, Birmingham, Ala.*): ROLE OF HYPERGLYCEMIA AND CARBON DIOXIDE IN THE REACTION TO STRESS. Endocrinology *54*:425-30, April 1954.

Exposure of fasting rats to an oxygen tension equivalent to an altitude of 20,000 feet resulted in a drop in the blood sugar of up to about 20 per cent with a return to normal within 4 hours followed by an increase in blood sugar of about 20 per cent at the end of 24 hours.

Rats stressed by exposure to cold showed reduction in the adrenal ascorbic acid, cholesterol, and eosinophils which could be partially blocked if the stress was carried out in an atmosphere of 5 per cent carbon dioxide.

Levin, Marvin E. (*Washington Univ. Sch. of Med. & Barnes Hosp., St. Louis, Mo.*): SPONTANEOUS REMISSION OF DIABETES MELLITUS: "THE HOUSSAY PHENOMENA IN MAN." Ann. Int. Med. *40*:1230-34, June 1954.

A 56-year-old man who suffered a cerebrovascular accident after 15 years of insulin-treated diabetes, subsequently developed cold intolerance, less perspiration, loss of libido and repeated hypoglycemia despite reduction of the dosage of insulin from 50 to 20 units (protamine zinc insulin). Finally he remained aglycosuric on dietary restriction alone. In addition to this clinical evidence of hypopituitarism, his urinary FSH was 0. The eosinophil response after epinephrine and ACTH was normal. Maintenance therapy consisted of 12.5 mg. cortisone, 30 mg. thyroid, and 10 mg. methyltestosterone linguet daily until death from another cerebral accident.

Eight other cases of remission of diabetes after development of hypopituitarism have been reported.

Levin, Noah B. (*The Chicago Med. Sch., Chicago*): DIABETES IN INFANCY AND CHILDHOOD. Chicago Med. School Quart. *15*:49-55, Spring 1954.

Juvenile diabetes is usually a severe form of the disease, with a tendency to marked instability characterized by frequent swings between insulin reactions and prominent degrees of glycosuria. Complete control of symptoms will be accompanied by physiologic conditions reasonably close to normal, with absent or minimal glycosuria. This can be achieved by permitting the patient a free diet, with limitation only of free sugars. This method of treatment can insure both good clinical and chemical control, and will defer and limit the development of arteriosclerotic complications.

Lowe, K. G.; Moodie, G.; and Thomson, Margaret B. (*Dept. of Med., Univ. of St. Andrews and the Dept. of Biochem., Univ. Coll., Univ. of St. Andrews*): GLYCOSURIA IN ACUTE TUBULAR NECROSIS. Clin. Sc. *13*:187-97, May 1954.

Glycosuria in excess of 20 mg. per 100 ml. with normal blood sugar levels, is pathological and probably indicative of a renal tubular lesion as it is not caused by osmotic diuresis. Such glycosuria is known to occur in acute and chronic poisoning of renal tubular epithelium and is shown to occur in acute tubular necrosis of renal ischemic origin.

Lowrey, George H.; Graham, Bruce D.; Tsao, M. U. (*Dept. of Pediatrics and Communicable Diseases, Univ. of Michigan, Ann Arbor, Mich.*): CHEMICAL HOMEOSTASIS IN THE NEWBORN INFANTS OF DIABETIC MOTHERS. Pediatrics *13*:527-35, June 1954.

Except for better control of diabetes in the mother, there is no known method to reduce the infant mortality rate, which remains very high, approximately 30 per cent. Likewise there is at present no completely adequate explanation for this poor prognosis. The present study of the blood electrolyte balance was undertaken to elucidate certain points in the physiology of the newborn infant of a diabetic mother. The 11 infants studied had extremely variable plasma chloride and total base levels, and a high proportion of these had an uncompensated acidosis with a lowered blood *p*H when compared to the normal newborn infant. The high plasma carbon dioxide tension indicates that ventilatory control of this factor was lacking, whether the fault be central or pulmonary.

Furthermore, there appears to be a direct correlation between the degree of acidosis and the severity of the abnormal clinical picture present. The exact cause of this acidosis is not at present clear.

Luntz, George (*Diabetic Unit, Romsley Hill Hosp., Halesowen, England*): TUBERCULOSIS DIABETICS: THE BIRMINGHAM REGIONAL SERVICE. Lancet 1:973-75, May 8, 1954.

The case of diabetes with a complicating tuberculous infection is unsuitable for domiciliary treatment. The detailed attention required for careful management of these two diseases cannot be given except in a special hospital unit with adequate laboratory facilities; and, moreover, there should be no delay in providing inpatient treatment for the newly diagnosed case, which is a medical emergency. It is all too common to find that diabetics who are admitted to a sanatorium for the treatment of a complicating tuberculous infection have their diabetes inadequately treated, with serious consequences. These patients need the close supervision of a physician experienced in the management of both diseases and they also need specialized nursing care.

Major, James W.; and Ottenheimer, Edward J. (*Yale University Sch. of Med., New Haven, Conn.*): PANCREATITIS. Am. J. Nursing 54:722-23, June 1954.

The authors review the salient features of pancreatitis, including its types or phases, pancreatic function, known causes of pancreatitis, differential diagnosis, and medical and surgical management.

Markovitz, Meyer (*Dept. of Med., Univ. of Illinois College of Medicine, Chicago, Ill.*): COEXISTING DIABETES MELLITUS AND ADDISON'S DISEASE—REPORT OF TWO CASES. Metabolism 3:268-73, May 1954.

Thirty of the 41 cases reported with the combination of these diseases are well documented.

The first case is that of a female who developed diabetes controlled with protamine insulin nine months after the removal of her thyroid for a fetal adenoma and chronic thyroiditis. Three years after onset of diabetes, unusual tanning was noted and four to six months later, when she went into shock after being aglycosuric for one month without insulin, the diagnosis of adrenal cortical insufficiency was made. Management consisted of oral cortisone, hypodermic desoxycorticosterone, and NPH insulin on which she was partially restored to useful life.

The second case is a 31-year-old male with diabetes of 14 years and Addison's disease for five years when first seen in 1944. Laboratory proof of adrenal disease was lacking but clinically he had hypotension, pigmentation, gastrointestinal symptoms and marked insulin sensitivity. He died in shock, possibly of hypoglycemic origin. Tuberculosis of the adrenal glands was the probable cause of the Addison's disease.

Mayer, J.; and Barrett, R. J. (*Boston, Mass.*): SENSITIVITY TO COLD IN THE HEREDITARY OBESE-HYPERGLYCEMIC SYNDROME OF MICE. Yale J. Biol. & Med. 26:38-45, September 1953.

Mice with the hereditary syndrome of obesity and hyperglycemia are extremely sensitive to cold and die of exposure in a few hours. This is in contrast to the marked resistance of the nonobese animals, even when these are fasted or fasted and exercised.

Pharamacologic doses of thyroxine, thyrotropic hormone, or dinitrophenol prolong significantly, but not considerably, the life of hereditarily obese-hyperglycemic mice exposed to cold. Corticotropin shortens duration of survival under the same conditions.

Death occurs in obese animals before nonobese controls show any signs of cortical or thyroid hypertrophy.

It appears probable that sensitivity to cold is not due to an impairment of cortical or thyroid function but is due to a primary block in fat utilization. The concept of lipophilia is discussed.

Mayer, J.; Marshall, N. B.; Vitale, J. J.; Christensen, J. H.; Mashayekhi, M. B.; Stare, F. J. (*Dept. of Nutrition, Harvard School of Public Health and Dept. of Physiology, Harvard Medical School, Boston, Mass.*): EXERCISE, FOOD INTAKE AND BODY WEIGHT IN NORMAL RATS AND GENETICALLY OBESE ADULT MICE. Am. J. Physiol. 177:544-48, June 1954.

When mature rats accustomed to a sedentary existence were exercised in a treadmill for increasing daily periods, it was observed that for low durations of exercise (20 minutes to one hour) there was no corresponding increase in food intake. Actually food intake decreased slightly but significantly. Body weight also decreased.

For longer durations of exercise (1 to 5 or 6 hours) food intake increased linearly and weight was maintained. For very long durations of exercise, the animals lost weight, their food intake decreased, and their appearance deteriorated. These three ranges of activity might be termed sedentary, normal, and exhausting. Both the sedentary and the exhausting ranges can be considered 'nonresponsive ranges' with respect to food intake as, in these ranges, an increase in activity is not accompanied by a corresponding increase in food intake.

When nonobese and genetically obese mice all accustomed to a sedentary exercise were exercised on a treadmill for one hour a day, and changes in weight compared to those of nonobese and obese mice not exercised, it was found that exercise did not affect the weight of the normal mice but considerably decreased the weight gain of obese mice even though these obese mice responded to exercise by an increase in food intake. Comparison of reactions to exercise of rats and mice show that there are some species differences in degree of reaction to exercise of normal animals; similarly, comparison of reactions to exercise of genetically obese and goldthioglucose mice show that there are differences in degree of reaction to exercise in different types of obese animals. The importance of considering exercise as well as food intake in problems of obesity is again illustrated by these results.

McArthur, J. W.; Gautier, E.; Swallow, K. A.; Godley, A.; MacLachlan, E. A.; Terry, M. L.; Hume, D.; Crepeaux, J.; Simeone, F. A.; Keitel, H.; and Berman, H. (*Massachusetts Gen'l. Hosp. and Harvard Med. Sch., Boston, Mass.*): STUDIES CONCERNING THE ROLE OF THE ADRENAL CORTEX IN THE PATHOLOGIC PHYSIOLOGY OF DIABETIC ACIDOSIS. II. THE IDENTIFICATION OF ADRENAL-CONDITIONED FACTORS IN THE PHYSIOLOGIC REACTION TO THE STRESS OF INSULIN DEPRIVATION. J. Clin. Investigation 33:437-51, March 1954.

The metabolic changes which characterized the stressful terminal phases of insulin deprivation in the depancreatized dog have been compared with: (a) the changes which accompany the induction of a comparable degree of eosinopenia by the administration of corticotropin to a depancreatized dog deprived of insulin for a comparatively brief period; and (b) the changes which accompany the withdrawal of insulin from an adrenalectomized-depancreatized dog maintained upon a fixed dose of adrenal cortical hormones.

The administration of corticotropin under these circumstances was found to result in a premature exacerbation of the diabetic state and in the appearance of a complex of metabolic phenomena characteristic of experimental diabetic acidosis resulting from prolonged insulin deprivation.

The withdrawal of insulin from an adrenalectomized-depancreatized dog maintained on a fixed dose of adrenal cortical hormones resulted in diminution or suppression of a number of components of pure insulin-deprivation acidosis.

McArthur, J. W.; Smart, G. A.; MacLachlan, E. A.; Terry, M. L.; Harting, D.; Gautier, E.; Godley, A.; Swallow, K. A.; Simeone, F. A.; Zygmuntowicz, A.; Christo, E.; Crepeaux, J.; Point, W. W.; and Benson, J. A., Jr. (*Massachusetts Genl. Hosp., Harvard Med. Sch., Boston, Mass.*): STUDIES CONCERNING THE ROLE OF THE ADRENAL CORTEX IN THE PATHOLOGIC PHYSIOLOGY OF DIABETIC ACIDOSIS. I. TEMPORAL RELATIONS BETWEEN THE METABOLIC EVENTS OF EXPERIMENTAL DIABETIC ACIDOSIS AND THE LEVEL OF ADRENAL CORTICAL FUNCTION. J. Clin. Investigation 33:420-36, March 1954.

The temporal relation between adrenal hyperactivity and other metabolic phenomena has been investigated in depancreatized dogs during the evolution of experimental diabetic acidosis by comparison of serial eosinophil counts and urinary corticosteroid determinations with (a) estimations of blood and urine chemical constituents, (b) balance measurements, and (c) changes in insulin sensitivity.

Eosinopenia and an increase in the rate of corticosteroid excretion were found to be comparatively late features of ketoacidosis induced by the omission of insulin.

A close temporal relation was found to obtain between increased adrenal activity, as judged by these indices, and the following metabolic events: (a) an acceleration in the rate of catabolism of protoplasm, manifested by an increased negativity of the nitrogen, potassium, and phosphorus balances; (b) a loss of potassium in excess of nitrogen, presumably from the cells of the body as a whole; and (c) a decrease in sensitivity to injected insulin.

An increase in lipemia and, in some instances, of ketonemia was observed to occur in association with evidence of adrenal activation. However, inasmuch as the blood levels of both lipids and ketones had begun to rise before eosinopenia became manifest, the temporal relation must be regarded as equivocal.

Meroney, W. H.; and Herndon, R. F. (*Army Med. Serv. Graduate Sch., Walter Reed Army Medical Center, Washington, D. C.*): THE MANAGEMENT OF ACUTE RENAL INSUFFICIENCY. J.A.M.A. *155*:877-83, July 3, 1954.

The plasma potassium level may be reduced by the infusion of a hypertonic dextrose solution. Results similar to those of a dextrose-insulin combination could be expected from the use of fructose, which does not require insulin for its early metabolism, but this sugar was not used. If dextrose is to be used effectively by the intravenous route, it should be given continuously. Intermittent intravenous injection of dextrose causes a sharp rise in the blood sugar level followed by hypoglycemia. (The hypoglycemic period has the double disadvantage of failure to remove potassium during that period and provocation of glycolysis with further release of potassium to the plasma.) Also, if nutrition is limited to intermittent intravenous feedings of dextrose, the period between infusions is one of relative starvation, which is characterized by cell destruction and release of potassium.

Moseley, V.; McCord, W. M.; Baroody, N. B.; Weeks, W. H.; and Ivester, Mary E. (*Depts. of Med. & Chemistry, The Med. College of South Carolina, and The Roper Hosp., Charleston, S.C.*): EFFECT OF ACETAZOLEAMIDE (DIAMOX) ON GLUCOSE TOLERANCE. Proc. Soc. Exper. Biol. & Med. *86*:498-500, July 1954.

Two glucose tolerance tests were performed on each of fourteen subjects (nine oral glucose tolerance tests, five intravenous glucose tolerance tests). The first glucose tolerance test was used as a control. A second test was performed 2½ to 3½ hours after the administration of acetazoleamide. These tests showed a tendency for the acetazoleamide to increase the oral glucose tolerance. The administration of acetazoleamide 2½ to 3½ hours prior to the intravenous administration of glucose did not result in as marked a degree of change in the glucose tolerance curve. After administration of acetazoleamide to patients receiving oral glucose tolerance tests a diminution of the urinary potassium excretion was observed.

Naide, Meyer (*Vascular Section, Robinette Foundation, Hospital of Univ. of Pa., Philadelphia, Pa.*): PREVENTION OF GANGRENE IN ISCHEMIA OF THE FOOT BY A PROTECTIVE COATING. J.A.M.A. *155*:746, June 19, 1954.

The use of compound tincture of benzoin is described as a protective coating for ischemic extremities, in which gangrene is threatening as the result of an impending break in the skin. Fragile skin can be protected in a simple and effective manner by coating it with this substance. Ointments, such as wool fat and cacao butter or olive oil, are not protective agents and often do not prevent gangrene, although they are of value in softening excessively dry skin. It has been found that a better protective coating is obtained for this purpose if compound tincture of benzoin is used in a more concentrated form than that described in the Pharmacopeia of the United States.

One hundred twenty patients with severe ischemia of the feet have required the use of compound tincture of benzoin as a protective coating during a period of two years. The sites most exposed to pressure, the first and fifth toes and the heels, are the areas that require most frequent protection of the skin.

Newcomb, Alvah L. (*Northwestern Univ., Evanston, Ill.*): DIAGNOSING AND TREATING DIABETES MELLITUS IN INFANCY AND CHILDHOOD. Mississippi Valley M. J. *76*:158-59, July 1954.

The basic principle underlying the treatment in infants and children is thorough education of their parents. Their parents should know: (1) the uses of the different insulins; (2) diet prescriptions; (3) how to perform urinalysis; (4) how to recognize and prevent complications; and (5) how to preserve the mental health of the child.

The controversy over the aglycosuric weighed diet regime versus the free diet regime is less violent than it was some years ago, and the conflicting opinions have come closer together. Some workers believe that it has been proved that constant glycosuria accelerates degenerative disease, but the advocates of the free diet dispute this contention. The author believes in an aglycosuric weighed diet regime.

Ketosis and severe insulin shock can generally be prevented if adequate time is given to educating the parents and the patient at the initial hospital visit and at each subsequent visit. As Rippy says, "Survival is not enough; protective control must be continually strived for." It is especially important that parents of the diabetic child be aware of emotional instability and forestall emotional upsets. It has been found that psychiatric therapy is indicated in a larger number of diabetic patients than in the general population.

Olmsted, James M. (*Dept. of Physiology, University of Calif., Berkeley, Calif.*): CLAUDE BERNARD AND GLYCOGENESIS. J. Am. Dietet. A. 30:545-49, June 1954.

This article describes in detail the experiments and the influence on medicine of Claude Bernard and especially his experiments on carbohydrate metabolism and glycogenesis.

Petersen, V. Posborg (*Med. Univ. Clin., Municipal Hosp., Aarhus, Denmark*): THE INTERRELATIONSHIP OF THE INDIVIDUAL PLASMA PHOSPHOLIPIDS AND CHOLESTEROL IN HEALTH AND IN LONG-TERM DIABETES MELLITUS. Acta med. scandinavica *146*:375-83, September 3, 1953.

The results of a study of the individual plasma phospholipids and cholesterol from 88 patients with "long-term" diabetes mellitus and from 107 healthy control subjects are reported. The results obtained showed an increase in total phospholipids and cholesterol in "long-term diabetics" under 40 years of age. The increase in total phospholipid values was due to an increase in both lecithin, sphingomyelin, and cephalin. In "long-term diabetics" over 40 years of age, normal values for cholesterol and total phospholipids were found. The phospholipid fractions displayed a slight shift in sphingomyelin and cephalin, but the lecithin concentration was within normal limits. The ratio of total phospholipids to total cholesterol did not differ between the diabetic and the control group. The plasma lipid pattern in diabetics with no or minimal retinopathy did not differ from that found in diabetics with severe retinopathy. The author concludes that the plasma lipid pattern in patients with "long-term" diabetes displays abnormalities, which are different from those observed in nondiabetics with atherosclerosis, and it is suggested that generalized diabetic vascular disease and atherosclerosis may be the result of different metabolic abnormalities.

Phibbs, Brendan (*Casper, Wyo.*): DIABETIC LIPEMIA: CLINICAL SIGNIFICANCE OF THE NEWER KNOWLEDGE. Rocky Mt. M. J. 50:876-79, November 1953.

Observations of lipemia and uncontrolled diabetes are presented. It is also noted that the lipid deposits in the arterial walls of diabetics are chemically similar to circulating lipids. This may indicate that the intima is freely permeable to these fatty substances. It is believed that disordered fat and carbohydrate metabolism are closely related in the diabetic. The fatty substances are divided into cholesterol, the phospholipids, the triglycerides, and neutral fats.

The work of Hirsch in relation to the "lipid-tolerance test" is considered. It was found that, in diabetes, as the blood sugar level rose, the level of lipids in the blood also rose and as the diabetes was brought back into control, the level of lipemia also fell. It was also found that the lipid-tolerance curve became more abnormal as hyperglycemia was induced. A discussion of these facts in relation to clinical control of diabetes is presented.

Rinehart, J. F.; Toreson, W. E.; and Abul-Haj, S. K. (*Dept. Pathology, Univ. Calif. Sch. of Med., San Francisco, Calif.*): HISTOCHEMICAL STUDIES OF THE HYALINE ISLETS OF DIABETES. Am. J. Med. *17*:124, July 1954.

While hyaline alteration of the islets of Langerhans is found in approximately 40 per cent of cases of diabetes, the nature of the hyaline material is not understood. Using a colloidal iron staining technic, the material reacts in the manner of an acid mucopolysaccharide. Increasing accumulation of this substance eventually obliterates the cells of the islet. The derivation of the hyaline mucoid material is not known although it would appear to be derived from the endothelium rather than the epithelium. It is pointed out that even minor accumulations of such material might constitute a significant barrier to the release of insulin.

Root, Mary A.; Ellis, J.; and Staub, A. (*Lilly Res. Labs., Indianapolis, Ind.*): EFFECT OF GLUCAGON ON INSULIN HYPOGLYCEMIA. Proc. Soc. Exper. Biol. & Med. *85*:507-11, March 1954.

Experiments in rabbits and mice have demonstrated that the presence of glucagon in insulin solutions in ratios of from 1:100 to 1:1 did not influence the degree of hypoglycemia produced by the insulin, since the maximum hyperglycemic effect of the glucagon occurred within 15 to 30 minutes, while the maximum hypoglycemic effect of the insulin came between 30 and 90 minutes. Consequently, the potency of the insulin preparation, as determined by the mouse convulsion assay, was unaltered by glucagon. In these experiments both insulin and glucagon were given subcutaneously.

Rossiter, R. J. (*London, Canada*): FRUCTOSE IN DIABETES MELLITUS (CORRESPONDENCE). Brit. M. J. *1*: 987, April 24, 1954.

In a letter to the editor, Rossiter points out that mannose is slowly absorbed from the intestinal tract but when given intravenously is as well utilized as glucose and much better than fructose in preventing insulin hypoglycemia, that it disappears from the blood stream in the absence of insulin, can maintain life like glucose, and unlike fructose can restore to normal the electroencepholographic changes observed during progressive hypoglycemia in hepatectomized animals.

Runyan, John W., Jr.; and Kantor, Nathan (*Thorndike Memorial Lab., Boston City Hosp., Boston, Mass.*): METABOLIC OBSERVATIONS IN INSULIN-RESISTANT DIABETICS GIVEN INTRAVENOUS FRUCTOSE. J. Lab. & Clin. Med. *43*:615-19, April 1954.

In two cases of insulin resistance requiring 600 units and 495 units of insulin daily, respectively, infusions of fructose were given. Elevations in the pyruvic acid levels were similar to those expected in the noninsulin-resistant diabetic and the nondiabetic. This suggested that there was no defect in the metabolic pathway of fructose to pyruvic acid in the insulin-resistant diabetics studied.

Sagild, Uffe; and Ditzel, Jörn (*Baker Clin. Res. Lab., New England Deaconess Hosp., and the Joslin Clin., Boston, Mass.*): MORPHOLOGIC AND HEMODYNAMIC CHANGES IN THE SMALLER BLOOD VESSELS IN DIABETES MELLITUS. II. THE DEGENERATIVE AND HEMODYNAMIC CHANGES IN THE BULBAR CONJUNCTIVA OF NORMOTENSIVE DIABETIC PATIENTS. New England J. Med. *250*:587-94, April 8, 1954.

An evaluation of the vascular and hemodynamic changes in the bulbar conjunctiva of 150 diabetic and 90 nondiabetic subjects is presented. The characteristic changes in the diabetic patients were in the capillaries and in the venules. The most consistent findings in the diabetic subjects were elongation of the venous part of the capillaries, distention of the venules, and aggregation of the blood cells, with concomitant reduction of the blood flow. None of these findings are in themselves specifically correlated with the disease, but the combined morphologic and hemodynamic pattern in the young diabetic patient appears to be characteristic.

Salomon, Hugo (*Buenos Aires, Argentina*): ANTIALLERGIC ACTIVITY OF INSULIN. Prensa méd. argent. *41*:852-53, March 26, 1954.

Several cases of bronchial asthma have been treated with insulin and a high caloric diet to restore normal weight. After insulin administration an apparent relief and a complete disappearance of the asthmatic episodes were observed. A direct antiallergic effect is attributed to insulin in these cases.

Sarett, Herbert P.; and Snipper, Lawrence P. (*Mead Johnson Research Labs., Evansville, Ind.*): COMPARISON OF FRUCTOSE AND GLUCOSE IN THE DIET OF ALLOXAN-DIABETIC RATS. J. Nutrition *52*:525-40, April 10, 1954.

In alloxan-diabetic rats maintained on a diet containing either fructose or glucose, the authors have made certain observations. Diabetic animals kept on a fructose-containing diet excrete less urine and less urinary carbohydrate than do the same animals on a glucose-containing diet or other animals with comparable levels of blood sugar on the glucose diet. Approximately 5 per cent of the sugar excreted by the diabetic animals receiving the fructose diet is fructose. Diabetic animals on the diet containing fructose consume slightly less food and markedly less water than do comparable animals on the glucose-containing diet. The livers of the diabetic animals receiving fructose are significantly larger than those of the diabetic animals receiving the glucose diet.

Schermann, José; Netto, Manoel Barretto: CLINICOPATHOLOGIC STUDY OF A CASE OF PHEOCHROMOCYTOMA. Rev. Brasil. Cirurg. *24*:3, 1952. Abst. from Surg., Gynec., & Obst. *97*:165, August 1953.

Pheochromocytomas are tumors that appear in the medullary portion of the adrenal gland; their cells reproduce the structure of the pheochromocytes. These tumors are responsible for many cases of paroxysmal arterial hypertension.

A report is made of a patient suffering from an adrenosympathetic syndrome (vasomotor disturbances with paroxysmal or permanent arterial hypertension, which disturbances started after various kinds of stimuli such as emotion, change of position in bed, feasting,

sleep, or abdominal palpation. There was an abnormal glucose tolerance; the basal metabolism was +36.5 per cent. An adrenal tumor weighing 90 gm. was surgically removed. The basal metabolism fell to +16.5 per cent, and the glucose tolerance test and the tetraethylammonium bromide test were normal.

Shuman, Charles R. (*Temple Univ. Hosp. and Sch. of Med., Philadelphia, Pa.*): MANAGEMENT OF DIABETES MELLITUS IN PATIENTS UNDERGOING SURGERY. J.A.M.A. *155*:621-26, June 12, 1954.

The diabetic patient is considered a safe subject for any type of surgery when modern methods of anesthesia, fluid and electrolyte replacement, antibiotic therapy, and control of metabolism and nutrition are used. Such methods were employed in the management of 350 cases of diabetes in which operations were performed.

Cardiovascular disease and infection significantly increase the surgical risk in diabetic patients. The use of NPH insulin, along or together with other insulins, is advocated because of its rapid and prolonged action. In uncontrolled patients or in the presence of severe acidosis, insulin is given in doses determined by the degree of glycosuria until metabolism becomes stabilized. Intravenous feedings given before, during, and after operation, replace the carbohydrate content of the diet and also correct dietary deficiencies. Emergency surgery is performed whenever indicated, with no more than a brief delay for the institution of treatment when acidosis is present; further deterioration of the metabolic status has been found in the substitution of fructose for dextrose in intravenously administered solutions.

Fructose was substituted for intravenous feeding during and after operation in 20 cases. There has been no reduction in the insulin requirements of these patients, and in two of them marked hyperglycemia and glycosuria appeared postoperatively, requiring supplementary regular insulin at that time and a rapid increase in the NPH insulin doses during subsequent days. Present limited experience doses not indicate any advantages in its use as compared to dextrose. It is known that several pathways for its disposal are available, including conversion to glucose and to glycogen as well as oxidation to carbon dioxide and water. Clinical observations indicate that fructose solutions are utilized effectively by the postoperative diabetic patient but they have permitted no reduction of insulin dosage.

Shuman, Charles R.; and Gilpin, Sherman F. (*Temple Univ. Hosp. and Sch. of Med., Philadelphia, Penn.*): DIABETIC NEUROPATHY: CONTROLLED THERAPEUTIC TRIALS. Am. J. M. Sc. *227*:612-17, June 1954.

The authors report upon 37 cases in which there was objective evidence of diabetic neuropathy of varying severity, an incidence of 51.7 per cent in the patients studied. Approximately a third or 12 of the patients exhibited relief of symptoms and of objective signs solely under careful diabetic control. The more severe neuropathies, usually found in poorly controlled patients or after therapy of coma, which did not respond to adequate treatment of diabetes, were then subjected to trial with (a) vitamin B_{12}, (b) pregnant mammalian liver extract, or (c) adenosine triphosphate with thiamine or pantothenic acid. Vitamin B_{12} in an initial daily dose schedule either orally or intramuscularly of 30 *µg.* for 10 to 21 days, later increased to 100 and then to 1000 *µg.* daily, followed by injections twice weekly, failed to produce improvement in 12 patients. The pregnant mammalian liver extract (Biohepulin) was administered intramuscularly 5 cc. or 10 cc. daily for 10 to 14 days, then 5 cc. twice weekly for 4 to 6 weeks, and brought about no objective improvement in the neurologic disorder of 15 patients. Six patients received treatment with adenosine triphosphate 25 mg., together with thiamine 20 mg. intramuscularly twice weekly for 4 weeks in 3 instances. Four patients were treated with adenosine triphosphate 25 mg. and pantothenic acid 10 mg. twice daily for three weeks. No alteration in the objective manifestations of neuropathy was noted in either group; 2 of the 6 patients under thiamin showed subjective betterment.

Siliato, F. THE PATHOGENESIS OF DIABETIC RETINOPATHY (EXPERIMENTAL CONTRIBUTION AND GENERAL CONSIDERATIONS). Annali di ottalmologia e clinica oculistica, 79:145-56, March 1953. Abstr. from Am. J. Ophth. 37:305, February 1954.

Findings point to the importance of the altered fat metabolism in the pathogenesis of diabetic retinopathy.

Spitzer, John J. (*Dept. of Physiology, Florida State University, Tallahassee, Fla.*): COMPARISON OF THE LIPEMIA CLEARING AND THE ANTICOAGULANT ACTIVITIES OF HEPARIN. Am. J. Physiol. *177*:337-40, May 1954.

A comparison of physiological properties is made between the anticoagulant and lipemia-clearing activities of heparin. The two functions and the cofactors involved seem to be independent and different on the following bases: (a) Several substances are known to neutralize the anticoagulant effects of heparin, among others protamine, toluidine blue and neutral red. Of the latter three, only protamine is able to reverse the lipemia-clearing effects of heparin. (b) Several times as much heparin is required to act as an anticoagulant as is needed to clear alimentary lipemia. (c) The mere presence of heparin in the circulation does not necessarily produce clearing factor, although it increases clotting time (for example, in shock). (d) The reverse of c is also true. The liberated heparin during peptone shock may produce clearing factor without increasing the clotting time of the blood. (e) Intravenous administration of heparin increases the clotting time of the thoracic duct lymph, without the appearance of the clearing factor in the lymph. (f) The affinity of heparin for a number of substances investigated shows the following decreasing order: protamine → clearing factor cosubstances → toluidine blue and neutral red → anticoagulant cofactor. These results indicate that if heparin has a physiological importance at all (which is not decided yet), it may produce the lipemia-clearing factor and regulate lipoprotein metabolism rather than influence the coagulation system of the blood.

Stanton, Eugene R.; Jones, H. Walter, Jr.; Marble, Alexander (*New England Deaconess Hosp., Boston, Mass.*): COEXISTING DIABETES MELLITUS AND ADDISON'S DISEASE. A.M.A. Arch. Int. Med. 93:911-20, June 1954.

The studies here reported emphasize that, although diabetes mellitus and Addison's disease only rarely occur in the same patient, the clinical features are characteristic and recognition is important. With modern therapy both conditions can be successfully treated and a useful life made possible. Forty-six patients, 26 males and 20 females, have been reported to date. All but four have been recognized in the insulin era. The average age at the time of recognition of the diseases was 37.7 years, with extremes of 10 and 69 years of age. The average age at death (or at last report) was 41.7 years. The duration of diabetes at death (or at last report) averaged 6.9 years, and that of Addison's disease, 3.0 years. Thus, one deals primarily with diabetes complicated by Addison's disease, rather than the reverse. In only 11 cases was it reported that Addison's disease preceded diabetes; in 3 other patients the onset of the 2 conditions seemed to be about the same time.

Addison's disease developing in a diabetic is characterized by a diminution of the insulin requirement, with frequent hypoglycemic reactions. Weakness, fatigue, and Addisonian crises with characteristic electrolyte changes may supervene. In the differential diagnosis one must consider hypopituitarism, hypothyroidism, and disorders of the liver. The therapeutic problem posed by the coexistence of these two conditions is by no means insurmountable. Each is treated definitively with the appropriate substitution therapy. In combination with cortisone given orally, long-acting desoxycorticosterone preparations for intramuscular administration are especially useful. Unusual care must be taken in the presence of stress, such as infections and acidosis. It is to be hoped that by prolongation of life by careful treatment not only will patients benefit directly but greater understanding of the fundamental nature of both diseases may be obtained by observation of their interaction over years of time.

Sturtevant, F. M.; Calvin, L. D.; and Fuller, N. E. (*Div. of Biolog. Res., G. D. Searle & Co., Chicago, Ill.*): THE RELATIONSHIP AMONG GLYCOSURIA, FOOD INTAKE AND BODY WEIGHT IN ALLOXAN DIABETES. Metabolism 3:262-67, May 1954.

The spontaneous glycosuria, food intake, and body weight of a group of alloxan-diabetic rats were subjected to a multiple regression analysis. Removal of the effect of intake and weight reduced the variability in diabetic glycosuria by 88 per cent. Either intake or weight alone accounted for 84 per cent of the variability in glycosuria. An index of the severity of diabetes was calculated by dividing the daily glycosuria of each rat by the daily food intake. This index was not related to food intake or body weight and indicated that over 50 per cent of the available glucose consumed was excreted in the urine. It appears that the severity of alloxan diabetes in rats is fairly constant.

Suárez, Ricardo Correa; and Rodríguez, Rafael (*Hospital de Enfermedades de la Nutrición, México, D. F.*): VASCULAR COMPLICATIONS IN DIABETIC PATIENTS. Rev. invest. clin. 5:273-96, July-September 1953.

In a group of 1066 diabetic patients vascular complica-

tions were observed in 38.08 per cent. Complications were observed within the first five years of the course of the diabetes in 24.49 per cent of the patients. This is probably due to the fact that patients did not receive treatment, or treatment was inadequate prior to admission to the hospital. Incidence of vascular complications increased in proportion to the duration of diabetes. Vascular complications were more frequent in the obese patients. The greatest number of complications were seen in diabetes requiring less than 10 units of insulin with 150 to 200 gm. of carbohydrate in the diet.

Taylor, William E.; Caughran, Katherine; and Hill, Barbara (*Springfield, Mo.*): DIABETIC DETECTION SURVEY DURING ENTRANCE PHYSICAL EXAMINATIONS AT A SMALL COLLEGE: PRELIMINARY REPORT. J. Lancet 74:247-52, July 1952.

Diabetes detection in conjunction with routine entrance examinations of college students is done best by using a micro blood sugar screening method, plus a routine test for sugar in the urine, followed up by a standard glucose tolerance test. Quite a few students will show abnormal urine and blood findings that cannot be diagnosed as either diabetes mellitus or renal glycosuria; some may be potential diabetics. All students with abnormal findings should be rechecked at later dates with repeated glucose tolerance tests. Of the 819 students examined, 5 had definite diabetes mellitus, 3 of these discovered by this survey. These blood sugar tests should become eventually as commonplace as our required chest roentgenograms and urinalyses.

Tolstoi, Edward (*Dept. of Med., New York Hosp. and Cornell Univ. Med. College, New York, N. Y.*): THE TREATMENT OF DIABETIC ACIDOSIS AND DIABETIC COMA. J. Kansas M. Soc. 55:1-7, January 1954.

Patients with diabetic acidosis or diabetic coma can be successfully treated with small and frequently repeated doses of regular insulin, replacement of water, salt and glucose by mouth, vein, or both. Data are presented to support the author's thesis that the administration of glucose by vein or orally is beneficial and not harmful. He does not use potassium salts routinely in the treatment of diabetic ketosis and coma; they have a definite value, but there are hazards associated with their use.

The author considers it unnecessary to follow the blood sugar and the carbon dioxide combining power as guides of therapy. In his experience, the clinical response and disappearance of ketone bodies are excellent guides. The earlier the treatment is begun, the more favorable is the prognosis, and, exclusive of medical complications, it can be stated categorically that the longer the patient remains unconscious, the less favorable are his chances for recovery.

Trumper, Max, Ph.D. (*National Agricultural Coll., Bucks County, Penn.*): HYPOGLYCEMIA: CLINICAL AND EXPERIMENTAL. M. Clin. North America (Chicago Number) 277-90, January 1953.

The author presents information on hypoglycemia from both a clinical and experimental viewpoint. A brief resume is made of glucose absorption and glucose metabolism and the effect of starvation on diabetes.

From the experimental viewpoint, hypoglycemia is discussed in relation to hydrazine poisoning. Underhill's work in the pre-insulin era is reviewed in some detail, and its possible importance today in producing hypoglycemia is stressed with the more widespread use of hydrazine derivatives today.

Van Itallie, Theodore B.; Morgan, Mary C.; Cathcart, Richard T.; Leduc, Gilles G.; and Dotti, Louis B. (*Dept. of Med., St. Luke's Hosp., New York, N. Y.*): PERIPHERAL ASSIMILATION OF FRUCTOSE IN MAN. Proc. Soc. Exper. Biol. & Med. 84:713-15, December 1953.

Serial peripheral arteriovenous fructose differences were measured in ten human subjects receiving a constant intravenous infusion of 10 per cent fructose in water (0.58 gm. per min.), following an initial priming injection. Maintenance of consistent and appreciable arteriovenous differences (10 to 13 mg. per 100 cc. at average arterial levels of 54 to 57 mg. per 100 cc.) were interpreted as evidence for direct assimilation of fructose by the peripheral tissues.

Venning, G. R. (*Univ. Dept. of Med., Manchester Royal Infirmary*): THE INSULIN-ZINC SUSPENSIONS. Lancet 1:480-86, March 6, 1954.

A trial of insulin-zinc suspensions in the management of acute diabetes is described. Most of the patients were outpatients who were studied in detail while they carried

on with their normal activities. There is no reason to believe that any mixture of different proportions of amorphous and crystalline insulin-zinc suspensions would provide satisfactory control in a higher proportion of diabetics than the 3 to 7 mixture at present available as insulin lente. The hypoglycemic action of insulin-zinc suspension seems to be more even and less erratic than that of preparations previously available. Local allergic reactions have been noted by two patients taking large doses of insulin-zinc suspensions. The preliminary impression that hypoglycemic reactions are less frequent and less severe than with soluble insulin has not been entirely confirmed by further observations. A few unexplained and sudden reactions have occurred in the latter part of the day in patients previously well controlled.

Villee, Claude A. (*Harvard Med. Sch., Boston, Mass.*): INTERMEDIARY METABOLISM. New England J. Med. *251*:21-28, July 1, 1954, and *251*:64-70, July 8, 1954.

This review has attempted to present some of the recent changes in concepts of the pathways of intermediary metabolism. An understanding of these pathways is fundamental to the rational treatment of metabolic disorders such as diabetes mellitus, pernicious anemia, gout and arteriosclerosis.

Wertheim, Arthur R.; Eurman, Gerald H.; and Kalinsky, Helen J. (*Goldwater Memorial Hosp. and the Coll. of Physicians and Surgeons, Columbia Univ., New York, N. Y.*): CHANGES IN SERUM INORGANIC PHOSPHORUS DURING INTRAVENOUS GLUCOSE TOLERANCE TESTS: IN PATIENTS WITH PRIMARY (ESSENTIAL) HYPERTENSION, OTHER DISEASE STATES, AND IN NORMAL MAN. J. Clin. Investigation *33*:565-71, April 1954.

The intravenous glucose tolerance curves and the concomitant changes in the serum inorganic phosphorus level have been studied in thirty patients with essential hypertension, and twenty-two normotensive patients with a similar age distribution.

There is a lesser fall in the serum inorganic phosphorus level in the hypertensive than in the normotensive group. Phosphate curves in some of the hypertensive patients resemble those found in patients with diabetes mellitus. The difference in phosphate fall between normotensive and hypertensive individuals is statistically significant.

Werthessen, N. T.; Milch, Lawrence J.; Redmond, R. F.; Smith, Leland L.; and Smith, E. C. (*Dept. of Physiol. and Biochem., Southwest Foundation for Research and Education, San Antonio, and the Dept. of Pharmacol. and Biochem., USAF Sch. of Aviation Med., Randolph Field, Tex.*): BIOSYNTHESIS AND CONCENTRATION OF CHOLESTEROL BY THE INTACT SURVIVING BOVINE AORTA IN VITRO. Am. J. Physiol. *178*:23-29, July 1954.

In studies made upon whole aortas excised from calves and swine, the authors report that cholesterol can be concentrated within the aorta when maintained in vitro. The increase in concentration of cholesterol is related to the rate of consumption of glucose by the aorta. The utilization of labeled acetate demonstrates that during the period of concentration of cholesterol by the aorta, active biosynthesis of cholesterol is going on within the organ. Examination of the cholesterol content of various sections of the aorta indicates a progressive change in concentration along its length. The concentration of cholesterol per gram dry weight of tissue is minimal at the origin of the aorta, at the heart, and rises to a maximum at the bifurcation. There was no significant relationship discernible between the lipoprotein titer of the perfusate and the cholesterol concentration of aortas maintained in vitro. The aorta can synthesize cholesterol to such an extent that within a short period it can approximately double the concentration of cholesterol within itself. The data indicate that the cholesterol so concentrated is synthesized rather than obtained from the perfusing medium.

White, Priscilla (*Boston, Mass.*): DIABETES IN PREGNANCY. Rocky Mountain M. J. *51*:357, May 1954.

The problem of diabetes in pregnancy is still one of the debatable topics as far as many obstetricians and internists are concerned. Dr. White clearly presents her views and classification of pregnancies and the outline of hormonal therapy, with which she has been so successful over the past number of years. Her results are most challenging; she reports maternal survival of 100 per cent with fetal survival of 90 per cent. The importance of follow-up studies on the child of a diabetic mother is certainly one that should be given due consideration, and Dr. White has followed 105 such children.

Wilgram, George F.; Hartroft, W. Stanley; Best, Charles H. (*Banting and Best Dept. of Med. Research, Univ. of Toronto, Toronto, Canada*): ABNORMAL LIPID IN CORONARY ARTERIES AND AORTIC SCLEROSIS IN YOUNG RATS FED A CHOLINE-DEFICIENT DIET. Science *119*:842-43, June 11, 1954.

In 22 per cent of young male rats fed for 4 weeks a diet containing 30 per cent protein, 35 per cent fat, and relatively low in methionine (520 mg. per 100 gm. of food) the authors report the production of aortic and coronary vascular lesions which were marked by diffuse internal and medial lipid deposits and by frequently associated medial calcification with the aortic lesions. Whenever fat was demonstrable in lining endothelial cells, the latter were swollen. Many animals on the low-choline diet succumbed either to acute hemorrhagic renal lesions or to cardiac necroses. Usually the vascular and renal lesions were associated, but rarely aortic sclerosis was evident in the absence of significant renal damage. It is suggested the term lipotrophic may now be extended to include the prevention of the accumulation of abnormal (stainable) fat not only in the liver and kidneys but also in the heart and blood vessels of animals that exhibit these lesions when choline and its precursors are withdrawn from the diet.

Winsor, Travis (*Sch. of Med., Univ. of Southern Calif., Los Angeles, Calif.*): SKIN TEMPERATURES IN PERIPHERAL VASCULAR DISEASE: A DESCRIPTION OF THE THERMISTOR THERMOMETER. J.A.M.A. *154*:1404-07, April 24, 1954.

A new instrument for thermometric measurements is described. Three leads are applied to a single extremity: on the toe, on the ankle, and below the knee. Vasodilation is then produced by means of indirect body heating and administration of 2 ounces of whisky orally. Low temperatures of the toes with higher temperatures at the ankle and below the knee suggest obstruction of the digital arteries. Low temperatures of the toes and ankle and a higher temperature below the knee suggest popliteal obstruction. Low temperatures of the toes, ankle, and calf suggest obstruction of the femoral or iliac artery.

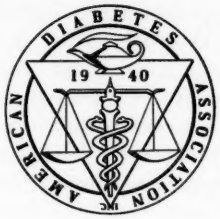
High grade organic disease generally exists, if, after vasodilation, no significant increase in skin temperature is produced and the temperature does not exceed 29°C. Characteristically, such disease states as Raynaud's disease, acrocyanosis, reflex sympathetic dystrophy, chronic phlebitis with vasospasm, trench foot, frostbite, and causalgia are primarily functional, while arteriosclerosis obliterans and arterial disease are primarily organic. A variable amount of functional vasoconstruction is present, however, in most cases of organic disease, and it is extremely important to estimate this functional component accurately in order to prescribe appropriate medical or surgical treatment.

Winter, W. D., Jr.; and Gellis, Sydney S. (*Beth Israel Hosp., the Children's Med. Center, the Joslin Clin., and the Depts. of Pediat. and Pathol. of the Harvard Med. Sch., Boston, Mass.*): PULMONARY HYALINE MEMBRANES IN INFANTS OF DIABETIC MOTHERS. Am. J. Dis. Child. 87:702-07, June 1954.

Microscopic sections of the lungs of forty infants born of diabetic mothers and dying in the neonatal period have been studied for the presence of hyaline membranes. Hyaline membranes were found in the lungs of three-fourths of the infants lacking some other major cause of death, but in only one-third of those with a major cause of death. The election of cesarean section was felt to be significant in increasing the incidence of pulmonary hyaline membranes in infants of diabetic mothers but appears justified in view of the high fetal mortality. Pulmonary hyaline membranes were believed to occur in the absence of and without relation to congestive heart failure.

Wishnofsky, Max (*615 Williams Ave., Brooklyn, N. Y.*): ULCER PATIENTS AND DIETS. J.A.M.A. *155*: 666, June 12, 1954.

After the ingestion of 100 gm. of dextrose and after the ingestion of 90 gm. of starch, the glycemia and glycosuria were identical in diabetics. The complete hydrolysis of 90 gm. of starch yields 100 gm. of dextrose. The digestion of starch, therefore, proceeds at such a rate that the amount of dextrose absorbed from the intestine per unit time when 90 gm. of starch is ingested is equal to the amount absorbed when 100 gm. of dextrose is ingested. Carbohydrate is the most potent stimulant of insulinogenesis; protein is much less so; fat is almost negligible. The fundamental principle in treatment, therefore, is to give a low-carbohydrate, a high-protein, high-fat diet. The nature of the carbohydrate—whether polysaccharide, disaccharide, or monosaccharide—is, from the practical standpoint, unimportant.



EDITORIALS

THE EFFECTS OF ADRENALECTOMY AND OF HYPOPHYSECTOMY ON THE DEGENERATIVE COMPLICATIONS OF DIABETES

In this issue of DIABETES appear three papers which report studies of the effects of total adrenalectomy or hypophysectomy on patients suffering from the degenerative complications of diabetes. In addition to the small number of patients whose cases are reported in these papers, a few other diabetic patients in this country and abroad suffering from retinopathy and intercapillary glomerulosclerosis have been treated by either adrenalectomy or hypophysectomy. Perhaps it is not too early to comment on the rationale and justification for the use of these radical measures in the study and treatment of the degenerative complications of diabetes.

There is good reason to believe that both diabetic retinopathy and intercapillary glomerulosclerosis are manifestations of the same degenerative vascular disease of diabetes. However, the pathogenesis of these complications is poorly understood, and most observers will concede that the rationale for their treatment by extirpation of the pituitary or adrenal glands is not entirely clear or well established. The two procedures are based in part on the hypothesis that certain hormones, particularly some of those secreted by the adrenal cortex, play either an active or a permissive role in the development of the degenerative complications. It has further been suggested that there are differences in adrenal cortical function of diabetics who have such complications as compared to those who do not.

The evidence in support of these hypotheses has recently been reviewed in DIABETES by Becker and associates.[1] Most of it is indirect or circumstantial in character, and supporting evidence in the field of clinical diabetes is still rather meager. Some clinical evidence is provided by a case reported by Poulsen[2] which has attracted wide attention. The patient was a young woman with diabetic retinopathy which healed completely following the development of pituitary insufficiency due to postpartum pituitary necrosis (Sheehan's syndrome). On the other hand, clinical evidence against a role of the adrenal cortex in the pathogenesis of the degenerative complications is the infrequency with which patients suffering from Cushing's syndrome, a condition characterized by chronic hyperfunction of the adrenal cortex, have anything resembling diabetic retinopathy or intercapillary glomerulosclerosis. Without reviewing all the available evidence, it appears that at present the conception that the anterior pituitary or adrenal cortex plays an active role in the development of the degenerative complications needs further support, although the possibility remains that the presence of these glands is a necessary condition for the development of the complications.

Regardless of what role the adrenal cortex and pituitary may play in the pathogenesis of the renal lesions of diabetes, the increased renal excretion of sodium chloride which uniformly follows adrenalectomy and sometimes follows hypophysectomy, might be of some benefit to patients with intercapillary glomerulosclerosis associated with hypertension and edema. Such benefit, however, does not imply a favorable modification of the underlying renal lesion.

It is to be hoped that some day a better understanding of the pathogenesis of the degenerative complications of diabetes will lead to methods for their prevention. In the meantime, the problem posed by these complications is of such great magnitude that further study of the role of the anterior pituitary and adrenal cortex is in order, and in selected otherwise hopeless cases exploration of such radical treatment as hypophysectomy and adrenal-

ectomy seems to be justified. The results to date must be viewed with conservatism, and the studies must be regarded as being in the field of clinical investigation of an illness for which there is no known effective method of treatment. Certainly any enthusiasm for the procedure in the far advanced type of case in which a radical approach to treatment seems most justifiable must be tempered by the realization that the lesions in the eyes and kidneys may already be essentially irreversible. Nevertheless, as of today, further experimental and clinical study of the whole matter seems desirable. Until the effects of hypophysectomy or adrenalectomy have been studied, it will be impossible to answer the practical question—do the results justify the means employed?

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2 Poulsen, J. E.: The Houssay phenomenon in man. Recovery from retinopathy in a case of diabetes with Simmonds' disease. Diabetes 2:7-12, Jan.-Feb. 1953.

HIGH REQUIREMENT FOR INSULIN FOLLOWING TOTAL PANCREATECTOMY

Human diabetes following total pancreatectomy is characterized for the most part by a low requirement for insulin, in the neighborhood of 40 units per day, and a rather marked sensitivity of its hypoglycemic effects. The small amount of insulin needed by these patients, compared with the much larger doses necessary in many with spontaneous diabetes, has been widely ascribed to the removal by pancreatectomy of the cells that make glucagon along with the cells that make insulin. The implication is that glucagon, the hyperglycemic-glycogenolytic factor, possesses physiologic activity and may, in the ordinary diabetic, either cause or mediate an increased need for insulin under certain conditions.

In the light of the foregoing, the recent report of Dituri[1] concerning insulin resistance after total pancreatectomy is of special interest. Following the operation the patient was discharged taking 20 units of protamine zinc insulin daily. Subsequently it became necessary to increase the dose to a maximum of 180 units, an amount which still failed to control glycosuria completely. Upon readmission to the hospital for further study, infection, endocrine abnormalities and aberrations of diet were eliminated as possible causes of this high requirement. Antibodies to insulin, however, were demonstrated in the serum.

This is the largest daily insulin dosage recorded for a depancreatized patient. Dituri cites two additional cases, both complicated by infection, with maintenance requirements higher than usual, namely, 84 and 50 units. Careful persual of other reports reveals that not uncommonly doses in excess of 40 units must be given for brief intervals. The patient of Greenfield and Sanders,[2] for example, subjected to dental extractions while on a daily dose of 40 units, developed ketosis with a blood sugar level of over 400 mg. per 100 cc. and received an extra 45 units over a period of 12 hours.

These observations are not entirely surprising in view of the known hyperglycemic effects of febrile disease and other forms of stress, operating presumably through the pituitary-adrenal axis, in both experimental and clinical diabetes. The contribution they make is to show that glucagon is not a necessary factor in the increased requirement for insulin that accompanies these conditions. The possibility is not excluded, of course, that glucagon, when present in the intact pancreas, participates in the aggravation of diabetes either as an independent agent or as a link in the chain of other hormones which oppose the action of insulin.

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THE STUDENT-INTERN ESSAY CONTEST

One of the major objectives of the American Diabetes Association is professional education. Every effort is made to convey to as many physicians as possible all that is

known about diabetes. The scientific programs of the meetings of the Association and its Postgraduate Courses bring authoritative information to those who attend. The Journal conveys this information to a larger share of the medical profession of this continent and abroad. The dissemination of information, however, is only a part of effective professional education. An interest in diabetes must be fostered.

The interest of practicing physicians in diabetes can be encouraged and increased by various means, including not only exposure to publications and lectures on the subject but also the demand for medical attention from the increasing numbers of diabetics among the population. Direct efforts to stimulate interest will pay the greatest dividends from the long-term point of view, if aimed towards the younger members of the medical profession. For this reason the Editorial Board of DIABETES considers the student-intern essay contest a project of high importance.

The first contest was announced in 1952. This contest and that of the following year brought forth papers of various types dealing with all aspects of diabetes and matters related directly or indirectly to diabetes. They have shown a high degree of constructive thought and effective study among medical students and young physicians. The third contest was announced in July. An award of $250 will be given to the author or authors of the best paper reporting original laboratory research or clinical study. An additional award of $50 will be given for the best review article or case report. The contest is open to medical students or physicians within two years of graduation. Other details have appeared in previous issues of DIABETES. Complete information will be furnished on request.

It is hoped that each year a larger number of young physicians will direct their study to diabetes and to the care of diabetic patients. In helping individuals with diabetes to maintain health and live successfully, each one can be assured of a reward beyond any monetary prize.

Milliequivalents

For many medical men who qualified more than a decade ago milliequivalents share some of the mystery that irrational numbers hold for the nonmathematical. But, simple units of measurement that they are, they have largely replaced such traditional though flexible units as milligrams per 100 ml. to record concentrations of ions. While readily convertible to metric units, their special features make them preferable for the estimation of the electrolytes of the plasma, which is becoming a commonplace laboratory investigation.

Milliequivalents are units of measurement no less than are the other, more familiar terms of metric weight; but they are units with this difference, that instead of being related arithmetically to other units of weight or volume within the metric system they imply a chemical relationship between the various ions under consideration. Thus, one milligram of sodium is not related to one milligram of potassium or one milligram of chloride except in so far as these amounts weigh the same, but one milliequivalent of sodium is chemically equivalent to one milliequivalent of potassium and to one milliequivalent of chloride and to one milliequivalent of bicarbonate, and in fact to one milliequivalent of any substance, although the actual weights of these amounts are not the same when expressed in milligrams. The equivalent weight of a substance is a chemical term defining that weight of the substance that will combine with or displace one gram-atom of hydrogen. A milliequivalent weight of a substance is its equivalent weight divided by 1,000, that is, the weight of the substance that will combine with or displace one milli-gram-atom of hydrogen. Adapting an old axiom, things that are equivalent to the same thing (in this case hydrogen) must be equivalent to one another, and it is this that justifies the use of the term milliequivalent in clinical chemistry today. Expressed in these terms, fluctuations in concentrations of electrolytes come to have some meaning in relation to one another. Calculation of concentrations expressed in milliequivalents per liter from those in milligrams per 100 ml. is done by multiplying the milligrams per 100 ml. by 10 to bring the concentration to milligrams per liter, and then dividing by the equivalent weight of the ion in question. The equivalent weight of the monovalent ions sodium, potassium, and chloride is equal to the atomic weight, namely, 23, 39, and 35.5 respectively. Some laboratories report the concentration of chloride in the form of sodium chloride, in which case the concentration in milligrams per 1,000 ml. must be divided by 58.5 and not by 35.5. Special factors have been calculated for the conversion of bicarbonate from volumes per cent and protein from grams per cent to milliequivalents per liter.

From the *Journal of the American Medical Association,* March 20, 1954.

BOOK REVIEWS

GLANDULAR PHYSIOLOGY AND THERAPY: *Prepared under the auspices of the Council on Pharmacy and Chemistry of the American Medical Association. $10.00, pp. 611, fifth edition, illustrated. J. B. Lippincott Company, Philadelphia, Pa., 1954.*

The fifth edition of this widely read text consists of twenty-two chapters written by thirty-one authors, all of whom are authorities in endocrinology. The chapter on the pancreas dealing with both diabetes and hyperinsulinism was contributed by Robert W. Schneider of the Cleveland Clinic. In its thirty pages, one finds a discussion of carbohydrate metabolism, the function of the islands of Langerhans including the alpha cell and the hyperglycemic-glycogenolytic hormone, the relationship of other endocrine glands, and clinical applications.

Other chapters concerned with specific endocrine glands which are particularly outstanding include: the adenohypophysis and the advances in knowledge of the anterior pituitary hormones and their effects on the gland; the physiology of menstruation and ovulation; the testes; the thyroid including its anatomy and physiology and hyper- and hypothyroidism; and the parathyroid glands. Chapters devoted to additional aspects of endocrinology, such as the endocrine management of neoplastic disease, diagnostic aids, chemistry of the hormones, abnormalities of body weight and common misconceptions in endocrine therapy are especially valuable and clearly written. For the reader who wishes to explore a particular topic further, an excellent, comprehensive bibliography is presented in each chapter.

The reviewer's only criticism of this book concerns the discussion of therapy in certain chapters. There is no discussion of treatment of the hypofunctioning and hyperfunctioning pituitary gland. The discussion of the treatment of acute and chronic adrenal cortical failure is not sufficiently specific and some of the methods of treatment presented are outdated. It is stated that there is no satisfactory treatment of Cushing's syndrome due to adrenal cortical hyperplasia; however, recent publications from two large clinics indicate that subtotal adrenalectomy followed by treatment with cortisone has produced satisfactory results. Since this book was prepared, descriptions of new methods to aid in the diagnosis of pheochromocytoma by biochemical, paper chromatographic, and fluorometric technics have been published.

Despite the increasing number of recently published texts on endocrinology, it is the opinion of the reviewer that this is one of the best single volumes for the medical student, the general practitioner, and the internist.

Terminology

The author has proposed the term *hypoproteinia* for the systemic deficiency of protein in the body, as differentiated from *hypoproteinemia,* denoting deficiency of blood proteins. The term *hypoproteinia* is analogous to *hypoxia* for deficiency of systemic oxygen, of which *anoxemia,* deficiency of blood oxygen, was the forerunner. The term *normoproteinia* has accordingly been proposed for a normal state of body proteins, although *euproteinia* would perhaps be just as acceptable.

The hypoproteinia caused by starvation may be called *primary hypoproteinia,* while that following disease and injury may be termed *conditioned hypoproteinia.* However, in accepting these modifiers, it must be remembered that hypoproteinia does not present as pure a picture as the deficiencies caused by the loss of specific nutrients. On the one hand, in starvation, the hypoproteinia is due not only to the inadequacy of protein intake, but also to insufficient caloric intake; body proteins are destroyed to supply the organism's caloric needs. This obligatory destruction of body proteins imposed by caloric needs becomes a "conditioning" factor. On the other hand, neither does the hypoproteinia following disease present a pure picture, since there is almost always the factor of insufficient intake of both proteins and calories.

The importance of protein in the body derives from the facts that (a) it is, next to water, the most abundant body constituent; (b) it forms the matrix of the cells, cytoplasm as well as nucleus; (c) it is inextricably involved in the maintenance of the integrity of the fluid compartments of the body as well as its tissues; (d) it plays an important role in immunological processes; and (e) it enters into the composition of the enzymes without which life is impossible.

These statements are only a more detailed itemization of the statements made years ago by Mulder and by Verworn.

From "Review: The Fundamentals of Clinical Proteinology" by Co Tui, M.D., in *The Journal of Clinical Nutrition,* March-April, 1953.

The Changing Outlook in Medicine

By Sir Henry Dale, London, England

Let me, in the first place, try to give some expression to my very deeply felt gratitude and my sense of the great honor which the American Diabetes Association has done me, in inviting me to give its annual Banting Memorial Lecture* this afternoon, and now, in bestowing upon me the Banting Medal. Be assured that I shall prize this Medal very highly, for more than one reason. I shall cherish it because, like the lecture, it commemorates Fred Banting, who, I am proud to think, was my friend —one whom I held in high personal regard, as well as in admiration and honor for the achievement which has meant health, happiness and life itself to so many already, and will continue to do so for many more in the future. And then I shall cherish it further on account of those who have given the Lecture and received the Medal before me—men whom I am honored to be able also to call my friends, and most of them distinguished, as I cannot claim to be, by contributions which they have individually made, with Banting, or in development of his discovery, to knowledge of diabetes and its treatment.

Earlier today, in the lecture commemorating Frederick Banting, I said something about the great stimulus which the discovery of insulin gave to what, at the time, was a relatively new movement in therapeutics, in which diseases due to different deficiencies, of hormones from the endocrine glands or of vitamins in the diet, came to be treated successfully by a direct replacement in each case of what was missing. This has, of course, grown into a major department of experimental research, and of the practical applications of the new knowledge thence arising. Quite clearly, however, it is only one aspect of a more general movement, which, within the memory of many who are still living, has been changing the whole outlook and aim of medical activity, whether in research, or in the practical use of its results. The introduction of the X rays in the last decade of the 19th century and later of the successive developments of radio-physics; the remarkable and still accelerating progress of biochemical and biophysical knowledge and methods: all these have brought an astonishing reinforcement to the resources available to medicine for diagnosis and prognosis. I myself, however, find it impossible to resist the conviction that the greatest and the most revolutionary change of all has been in the medicinal treatment of disease, which has, I believe, been more deeply affected than any other aspect of medical activity by the newly coöperative relation which has developed between the research work of the laboratories and the clinics, on the one hand, and the practice of the hospital ward and the physician's office on the other.

I do not think that anybody whose experience of these relations does not extend back to the opening years of the present century, when I myself was engaged in my all too brief and perfunctory clinical studies, can imagine how deep and complete at that time the division appeared to be, between clinical medicine and the experimental disciplines which, even then, had some distant hope of providing practical medicine with a scientific basis. In my own country at least, even the attempt to find such a relation received, at that time, explicit discouragement from the clinical side. When, as a student who had stayed at Cambridge for two additional years of postgraduate apprenticeship in physiological research, I entered the wards of St. Bartholomew's Hospital in London, I received an emphatic warning from the distinguished physician who was undertaking to teach me, or to try to teach me, some elements of clinical medicine. My first duty, he explained, on entering his ward was to forget all my physiology. Clinical medicine, he insisted, was still an empirical craft, having no relation to an experimental science like physiology. "Some day," he added, "we hope that medicine too may become an experimental science; but that is not yet." In many ways, let me explain, I admired such a man, for the complete candor of his attitude; there was something of the true spirit of science, and something which we can never afford to lose, in an attitude which said, in effect, "I am not going to accept any theory, or any indirect evidence from suggested analogy, unless it is in line with the direct experience which I have accumulated, during a

Delivered at the Banquet, 14th Annual Meeting of the American Diabetes Association in San Francisco on June 19, 1954.

* "Hormones of the Pituitary Posterior Lobe," the Banting Memorial Lecture, 1954, was given by Sir Henry Dale at the same meeting earlier that day. It will be published in the November-December issue of DIABETES.

lifetime spent in the observation of disease in my patients." That very candor and sturdy independence, moreover, induced and confirmed in such physicians an attitude of cynical pessimism with regard, especially, to the value of all but a very few of the drugs and medicaments, which their less critical colleagues were then so profusely and so confidently prescribing. Even for these enthusiasts, however, there was almost as complete a divorce between the practical therapeutics of the wards and the experimental pharmacology of the laboratories. "I believe that I have seen it do good in this condition," was for most of them a sufficient warrant for the continued prescription of a drug, even though no even plausible evidence could be found for its possession of any recognizable action or though pharmacological experiment had succeeded only in demonstrating one which could not reasonably be credited with any therapeutic value. Pharmacology, therefore, was scornful of the credulity and empiricism of clinicians, and of the tenacity with which they appeared to cling to therapeutic practices which had no apparent basis but tradition; while the clinicians replied, with some point as it seems to me, that, after all, healthy frogs do not necessarily show all the reactions of sick men.

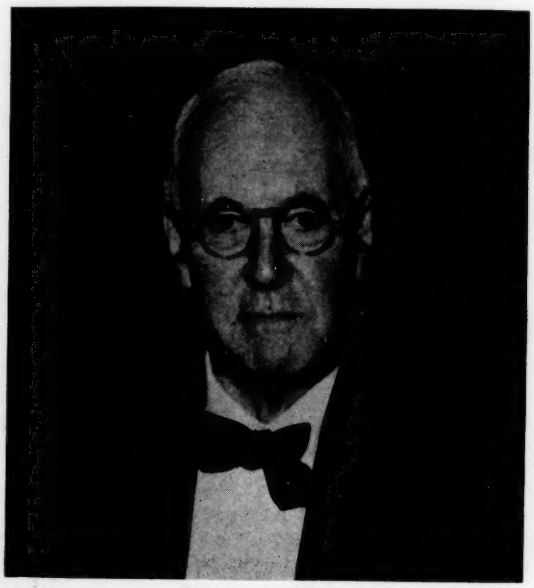
To be completely candid, I believe that the deep division, at that time, between medicinal therapeutics as practised, and experimental pharmacology as the subject of research and teaching in the preclinical departments, was due to faults on both sides. Whatever the cause, however, I do not think that anybody who remembers the position at that time can doubt that medicinal treatment was then in a poor way, and that it had, in fact, shown but little improvement for 100 years, or even more; some would have said, half seriously, for very many more. Friends of mine at St. Bartholomew's, most ancient of the London hospitals, used to recall an incident in the Staff Common Room there, one day after luncheon, when a member of the Staff, thoroughly steeped in the well-known pride of "Bart's" in its antiquity, was heard to remark in the familiar tone, that, after all, there was something impressive in the thought that, on that very site, the sick poor had been treated, without interruption, for more than eight centuries. "Yes, indeed," remarked another friend of mine, recently imported there as Professor of Pathology, and not yet fully acclimatized, "treated continuously for more than eight centuries, and largely by the same methods."

The best physicians, as I have suggested, had little use, but, on the contrary, a wholehearted contempt for all but a few of the remedies which tradition had handed down and which were still being freely prescribed; while the attitude of most of the experimentalists was of the humorously disrespectful type, of which I have just quoted an example. There was not wanting, on the other hand, a trenchant criticism, also from the experimental side, but aimed at the pharmacology then current, which, so far as it concerned itself at all with the interests of therapeutics, was largely occupied with attempts to discover, and to analyze by experiment, the activities of those drugs which the physicians were prescribing, seldom with any expectation of doing more than mitigate the symptoms of a disease, and help the patient thereby to survive, while nature dealt with the cause and was responsible for any cure which followed. The most vigorous and, I think, the most effective critic of this somewhat complacent pharmacology, as well as of most clinical treatment, especially of the diseases due to infections, was the late Paul Ehrlich, the centenary of whose birth was so recently being celebrated in Frankfort on the Main. He was certainly one of the principal leaders of the revolution which, in a few decades, was to change the central aim and the whole outlook of medicinal therapeutics, from the pessimistic, sceptical, tentative and merely palliative treatment of symptoms, to the effective and confident use of medicaments to suppress or to eradicate causes, which we see today. I myself believe, indeed, that posterity will judge the work of Paul Ehrlich to have had as important a transformatory effect on the medicinal treatment of disease, as that of Joseph Lister had had, half a century earlier, on its treatment by surgery.

Already at the beginning of the century, at the time when I myself was a student of medicine, there were some premonitory signs of the great change which was on the way. Nearly a decade earlier, in fact, there had been in one remarkable year, 1891, three separate events, each of which we can recognize in retrospect, I think, as preparing the way for the great change which was coming.

In that year Emil von Behring had discovered the formation of antitoxins, as accounting for the acquired immunity to diphtheria and tetanus; George Murray had discovered the first effective treatment of a deficiency disease by direct replacement—that of myxedema by giving thyroid gland; and Paul Ehrlich, with Guttmann, had performed the first experiment in the new campaign which he was to call "chemotherapy," by testing the therapeutic value of methylene-blue as a remedy for malaria. Chemotherapy was the direct search, as planned by Ehrlich, for new remedies, natural or artificial, which would deal with infectious diseases by directly attacking

the infective causes—remedies which would have an affinity, and a consequent toxicity, which would be maximal for the infecting parasites, and minimal for the organs and tissues of the patient. "If," said Ehrlich, "I ask the pharmacologist to tell me how quinine acts as a remedy for malaria, he cannot tell me. He tells me how it affects the function of a frog's muscle or a mouse's brain; and that is not what I want to know. I want to know by what specific action it removes the malarial parasites from the blood—how, in therapeutic doses, it cures my patient of his malaria, not how, in poisonous doses, it would injure or kill him; and the pharmacologist cannot tell me, and does not even try to. My quest for remedies better than quinine for malaria, or better than mercury for syphilis, or for remedies for other infections which are not yet treated at all, cannot then be called pharmacology." And so he called it by a new name, "chemotherapy."



SIR HENRY DALE

When I was a student, the antitoxin treatment for diphtheria and the thyroid treatment for myxedema, still ranking rather as novelties, stood out by themselves, against a general background of mostly symptomatic, or merely "expectant" treatment; and they stood out as remedies of a new kind, dealing directly with the causes of diseases. They were only indications of what was to come—early symbols of what would happen when the research laboratories and the wards were really in full and effective coöperation. But the new movement had not really started then. As I have already suggested, endocrinological therapeutics seemed to wait for the discovery of insulin to receive a fresh impetus. Ehrlich, to the lasting benefit of immunology, had been led, by his coöperation in realizing the practical, therapeutic application of the diphtheria antitoxin, into a decade of fundamental studies on the reactions of immunity, and on the immune antibodies, as the most specific of all chemotherapeutic agents, the real "magic bullets" of his dreams. And then, when he returned to the quest for artificial remedies, experimental infections with trypanosomes and spirochetes were ready to his hand, and he achieved with salvarsan, in 1911, the first major practical triumph for the new chemotherapy. It was followed by a rapid extension of successful chemotherapy to various protozoal infections, many of them responsible for diseases of the tropics; but, for another 25 years or so, the ordinary bacterial infections seemed to be inaccessible to it, till the sulfanilamide derivatives came, and then the antibiotics, and the whole outlook for the treatment of infections rapidly changed. More recently again, symptomatic treatment, most of it formerly so vague and tentative, has shared increasingly in the new relation of confident coöperation between the clinics and the research laboratories, and is conforming to the general direction of the new therapeutic aims, by dealing, not with primary causes, indeed, but with scientifically determined proximate causes of the symptoms, as in the case of the antihistamines. It seems to me indeed, looking back over more now than half a century of opportunity to observe the medical scene, and especially that part of it which is concerned with medicinal treatment, that it is hardly possible to exaggerate the magnitude of the change.

Fifty years ago, the best physicians appeared to concentrate their keenest interest on diagnosis; and they made a fine job of it, largely without the aid of any of the resources now available from neighboring fields of science. Today, with medicaments of such strong and varied scientific credentials, available to deal with the primary causes of disease, or with the recognized proximate causes of its symptoms, there seems to be a danger that the tables will be turned, and that the busy doctor will be in such a hurry to apply the really potent remedies now ready to his hand, that the consultant will be apt to find little on which to base a diagnosis, when the case arrives in hospital.

A physician practicing in London recently said to me, indeed, that his predominant concern was rapidly coming to be the recognition and treatment of the effects

of excessive dosage with the antibiotics.

Patients, for their part, are no longer, as formerly, sceptical of the value of medicinal treatment. On the contrary, they are becoming ever louder in their reproaches to medical research, for not having yet discovered specific cures for cancer, or poliomyelitis, or the common cold, and are ever more confident in the results to be expected from the earmarking charitable funds for researches specifically aimed at such discoveries. You may also have heard a story of the plight of a pharmaceutical manufacturer, who is said to have found it necessary to offer a prize for the discovery of a disease, on which the latest miracle drug from his research laboratories will act as a specific cure.

During my stay in this city, I have also been taking notice of some of the impressionistic accounts in the daily press, of meetings of the specialist medical societies which seem now to be swarming into San Francisco, in anticipation of the session of the American Medical Association, which is due to be held here next week. One communication, thus picturesquely reported, had a natural interest for me, as one who entered his eighth decade a few days ago, in that it dealt with a professedly effective treatment for the symptoms of senility: the ingredients of the treatment appeared to be a diet rich in proteins, which would suit me well enough, I think, combined with a varied array of hormones.

Speaking more seriously, this new era in medicinal treatment will assuredly pose new problems—economic, educational, administrative and other problems—and, like most other gains, its achievement will have entailed some loss, in this case of some of those things which were good in an older clinical tradition. But I ask you, with some confidence, whether any of you can seriously doubt that the gain, on balance, from this changing outlook in therapeutics, from this increasing intimacy of coöperation between research and practice in so many directions, has been immensely, immeasurably beneficial. Not least, in realized benefit and incalculable promise of more, has been the practical application of the growing wealth of knowledge produced by researches in endocrinology; and, having had the privilege of watching that development, as an interested onlooker, from its early beginnings, I am especially grateful for the opportunity with which your association has honored me, to speak of it as one aspect only of a much wider therapeutic revolution, in which, however, it has played one of the leading parts.

Aretaeus, the Cappadocian

History Enlightens the Present

John A. Reed, M.D., Washington, D. C.*

The late Joseph H. Barach, past President of the American Diabetes Association, presented me five years ago with his textbook on diabetes[1] and inscribed on the flyleaf, "To John Reed with whom, in medicine and in friendship, I am joyously tied to the same yoke." The first chapter of this book is entitled "History of the Disease" with a subtitle, "Men and Milestones." It is a brief thumbnail sketch of the history of diabetes, concisely written. His entire book combines the language of a scholar with the accuracy of a scientist. It is here that I first learned of Aretaeus and his place in the historical background of diabetes.

The material for this sketch of Aretaeus and his works is derived from the papers and books listed in the references.[1-8] Fascinating hours were spent in reading the original work of Francis Adams, LL.D. (1852),[2] which I was able to obtain through the Armed Forces Library, Washington, D.C., formerly known as the Library of the Surgeon General's Office. Adams, scholar and translator of the mid-nineteenth century, was commissioned by the Council of the Sydenham Society of London "to supply the profession with an improved text of the original, and a correct translation."

Of Aretaeus, personally, there is little direct knowledge other than that suggested by the title. It indicates possibly that he was a native, or at least a citizen, of Cappadocia, a mountainous country in the eastern part of Asia Minor bordering on the Euphrates, formerly an independent kingdom until it was conquered by the Persians during the reign of Alexander the Great. In A.D. 17 Cappadocia was conquered by the Romans and became a province of the Roman Empire. It is generally considered that Aretaeus lived in the second century of the Christian era, possibly between the time of Celsus (30 B.C.-A.D. 30) and the well-known Galen, who was born in A.D. 131. The exact period of his life is not known, but it is placed rather positively in the second century. This is based in part on the fact that he places considerable emphasis in his works on the Pneuma, the Spirit. The doctrine of the Pneuma goes back to Hippocrates, but it did not become the basis of a school until much later. Athenaeus of Sicily (A.D. 50) may be regarded as the founder of the Pneumatic School, which added the Pneuma to the four elementary qualities of the older schools and made it the source of life. Aretaeus is classed as a member of the Pneumatic School.

Little is known of the education of Aretaeus; it is believed that he studied at Alexandria and spent some time in Egypt. The time of his coming to Rome is unknown also, but his writings indicate a personal familiarity with Rome of the second century. Neither Celsus nor Galen mentions Aretaeus, while the latter speaks only of Hippocrates in his writings. That these fairly contemporary writers do not mention each other cannot be accepted as evidence that they were unknown to one another. Aretaeus and Galen may have been rival practitioners, and rivalry among medical men of that age was quite common. Also, it was very uncommon for living writers to quote any of their contemporaries by name because it was felt impossible to form an unbiased opinion on their work.

Adams says in his Editor's Preface, "It is deserving of remark that we have a still more extraordinary example of two contemporary authors under similar circumstances, mutually neglecting to quote one another, in the case of two writers who lived a short time before Galen, namely Dioscorides and the Elder Pliny." Dioscorides, the founder of materia medica, and the elder Pliny

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The cover picture of Aretaeus was furnished the American Diabetes Association by Burroughs Wellcome & Co. through the courtesy of Dr. Donald S. Searle of the American branch of the company.

were contemporaries, the former a prolific writer and the latter a great compiler. They wrote many works and discussed the same subjects, but neither names the other. Celsus (Aurelius Cornelius) was not actually a physician but a gentleman of a noble family of Rome. He compiled, or more probably translated, encyclopedic treatises on medicine as well as other subjects. Hence, it might well be that mention of Aretaeus by Celsus and Galen would not be expected. There is considerable similarity to be found in the writings, however, of Galen and Aretaeus, since both use Hippocrates as a model and have a partiality for the philosophy of Plato. Both display marks of similarity in recommended therapy. They do differ, however, in one striking manner, as pointed out by philologists. Galen wrote in the Greek of his day, the Attic Greek of Xenophon, while Aretaeus' known works are in Ionic Greek, which was used by Hippocrates but was long out of common usage when he wrote his works.

Aretaeus' claim to fame in the historical background of diabetes is well founded. All authors, certainly from the time of the very early English translations, and probably before this, clearly state that Aretaeus was the first to use the word "diabetes" in connection with this disease. His remarks concerning this name are interesting, for after noting that water goes through these patients, he concludes that the name is derived from the Greek word meaning "a siphon" and another Greek word meaning "to go through." Fielding Garrison,[6] a modern recorder of medical history, says this of Aretaeus: "As a clinician, Aretaeus ranks next to the Father of Medicine in the graphic accuracy and fidelity of his pictures of disease, of which he has given the classic accounts of pneumonia, pleurisy with empyema, diabetes, tetanus, elephantiasis, diphtheria, the aura in epilepsy, the first clear differentiation between cerebral and spinal paralysis, indicating the decussation of the pyramids, and a very full account of the different kinds of insanity."

Adams writes: "His descriptions of diseases have been universally admitted to be unsurpassed for elegance and accuracy. As a solitary proof of their value, I may mention that Hippocrates and Aretaeus are almost the only authorities among his predecessors in whose works Laennec detects any anticipations of his own system of diagnosis in diseases of the chest. In a word, no one can fail to perceive that he [Aretaeus] was gifted with the rare talent of giving a more striking delineation of a series of morbid phaenomena, in one page, than most authors would give in a long treatise."

The following is a clinical description of diabetes by Aretaeus, with certain portions omitted:

"Diabetes is a wonderful affection not very frequent among men, being a melting down of the flesh and limbs into urine. As with Hydrops, the cause is of a wet and cold nature. The kidneys and bladder, the usual passageways of fluid, do not cease emitting urine, and the outpouring is profuse and without limit. It is just as though the aqueducts were opened wide. The development of this disease is gradual, but short will be the life of the man in whom the disease is fully developed. Emaciation proceeds quickly and death occurs rapidly. Moreover, life for the patient is tedious and full of pain. The desire for drink grows ever stronger, but no matter what quantity [of fluids] he drinks, satisfaction never occurs, and he passes more urine then he drinks. He cannot be stopped either from drinking or from urinating. For if he be restrained even for a short time from drinking, the mouth becomes parched, the body dry, and they feel as though all their viscera were being consumed by a raging fire. They despair of all and death occurs shortly amid a burning dryness, thirst as if caused by a burning fire. . . . And when the disease is at its height they urinate constantly. From this fact, the disease has derived its name, 'diabetes,' meaning 'siphon,' for fluids do not remain in the body, but use the body only as a channel through which they may flow out. . . . The evil of the affliction is that thirst and drink increase one another. . . ."

The first report of Aretaeus' works occurs in the writings of Aetius of Amida, physician to Justinian the First (A.D. 527-65), who quotes him frequently. Alexander of Tralles and Paul of Aegina (A.D. 625-90), compilers and systematizers of medical knowledge, referred to his work.

Following this period of the recognition of the writings and works of Aretaeus there pass nearly a thousand years before any other mention is made concerning them. It is true that there was the decline of the Roman glory, and medicine was barren, but in this interval the Arabian school of medicine rose and likewise declined, followed by the school of Salernum and the great universities of Bologna and Montpellier, where there was great increase in the knowledge of anatomy and physiology and extensive section of the human body. But there is no mention of Aretaeus.

With the invention of the printing press and the rebirth of knowledge during the Renaissance, we find the earliest printings of the authors of antiquity beginning with the sixteenth century. The first edition of the

works of Aretaeus was published at Venice in 1552 by Junius Paulus Crassus. It was printed in Latin. The editor, in his preface, announced that the work in Greek, bearing the name of Aretaeus, the Cappadocian, had accidentally fallen into his hands, and that with great labor and care he had made his version, and published it, lest such valuable fragments, in so perishable a state as he found them, should be altogether lost. The next edition was reprinted in Paris in 1554, by William Morel and James Putianus. The *Edita Princeps,* the first edition in Greek, was published in Paris in 1554, edited by Jacobus Goupylus and printed by Adrian Turnebaum, the famous printer to King Henry II of France. In 1581, Crassus edited a revised edition in Latin, which contains many chapters missing in the first edition. It was printed by Peter Pernam.

The first Greek-Latin edition to be published was edited by George Heinisch and printed at Augsburg by Augustus Vindelicorum in 1603. This edition was a very poor one but was followed by the next Greek-Latin printing, edited by John Wigan and printed by the Clarendon Press of Oxford in London, 1723. This was based upon two manuscripts, one of which was in the Vatican Library at Rome and the other, the Harleyean, in the Bodleian Library at Oxford. It was carefully printed, full of notes, and a most excellent edition.

It is noteworthy that even in these early and first years of printing much attention was given to format and typography. Of this edition Adams states, "The performance is beyond all praise; for as to elegance and accuracy of typography, and all other embellishments of a classical edition, it is unsurpassed." Boerhaave stated that there were only three hundred copies of this particular book printed. Under the direction of Boerhaave, the next edition was published, edited by Johanan von Groenveld and printed by Janson Van der Aa at Leyden in 1731 and reprinted in 1735. It is in Greek and Latin, the former based on the Wigan edition and the latter on the Goupylus edition of Crassus' publication of 1581.

Following the Boerhaave edition of the works of Aretaeus, a number of others appeared, but probably only two are important enough to deserve mention. Francis Adams edited the first Greek-English edition, which was published by the Sydenham Society in 1856. Although some authors refer to Adams' work as the first English translation, actually there were two before his. Moffatt translated Aretaeus' works into English in 1785, and Reynolds did so in 1837. Adams' Aretaeus is a complete, thorough, and scholarly presentation. He says of his own work that "I have endeavored to prepare myself for my editorial duties by a diligent revision of all the Greek writers who used the peculiar dialect of Aretaeus, from Herodotus and Hippocrates down to Arian and Lucian. I trust, also, it will be seen indirectly, that I have not been remiss in availing myself of the distinguished labours of contemporary philologists, especially Dindorf and Daremberg, and the lexicographers of Oxford. Having bestowed so much pains on my work, I shall certainly feel some disappointment if it is not such as to satisfy the reasonable expectations both of the classical scholar and of the learned physician." The Danish philologist, Karl Hunde, edited a German translation published as a part of the monumental *Corpus Medicorum Graecorum,* printed in Leipzig in 1923. This is an elaborate and excellent edition.

Eugene F. Cordell, Professor of The History of Medicine at the University of Maryland,[7] stated in 1909 that the titles of the works of Aretaeus were as follows: On the causes of symptoms of acute and chronic diseases; on the therapeutics of the same; fevers; surgery; prophylaxis; diseases of women; pharmacy. Only the first and second are now extant. They comprise eight books, in a very mutilated condition, with whole chapters missing.

So wonderfully descriptive was Aretaeus' account of diabetes and other various diseases that Sir William Osler[8] wrote of him, "I doubt very much whether Corvisart in A.D. 1800 was any more skillful in recognizing disease than was Aretaeus in the second century A.D. When one has read the pages of this old master, one cannot help but be impressed greatly by the scholarly presentations of disease which he has left us."

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ORGANIZATION SECTION

Third Postgraduate Course in Diabetes and Basic Metabolic Problems

Philadelphia, Pennsylvania, January 19-21, 1955

The American Diabetes Association will hold the Third Postgraduate Course in Diabetes and Basic Metabolic Problems under the Directorship of Edward L. Bortz, M.D., Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, and Associate Professor of Medicine, Jefferson Medical College, Philadelphia, Pennsylvania. The Associate Director is Henry F. Page, Jr., M.D., Instructor in Medicine, Jefferson Medical College, and Instructor in Medicine, Graduate School of the University of Pennsylvania, Philadelphia, Pennsylvania. Members of the Local Committee on Arrangements are Angelo P. Angelides, M.D., Joseph T. Beardwood, Jr., M.D., Edward S. Dillon, M.D., Garfield G. Duncan, M.D., W. Wallace Dyer, M.D., Francis D. W. Lukens, M.D., and Joyce T. Sheridan, M.D.

The Course, which is open to the medical profession, will be held January 19, 20 and 21, 1955, at the new Lankenau Hospital, Philadelphia, Pennsylvania. Registration is limited and the minimal registration is 25.

FEES: $40 for the three-day Course for members of the American Diabetes Association; $75 for nonmembers. The full fee is payable at the time of filing application for the Course and will be returnable by the Association to any registrant who submits his withdrawal in writing not later than January 5.

REGISTRATION: An application form is attached to the preliminary program and should be filled out and mailed, together with the fee, as soon as possible. Registrations will be accepted in the order received with preference given to members of the Association. All registrations will be officially confirmed.

HOTEL ACCOMMODATIONS: The Bellevue-Stratford will serve as the headquarters hotel. Reservation forms will be sent to registrants with their matriculation card confirming acceptance for the Course.

THE FOLLOWING TOPICS AND DISCUSSIONS (SUBJECT TO CHANGE) WILL BE COVERED DURING THE 3-DAY COURSE.

TUESDAY EVENING, JANUARY 18

7:00 Registration
Lobby, The Bellevue-Stratford

WEDNESDAY MORNING, JANUARY 19

8:00 Registration
The Lankenau Hospital

9:00 Opening of the Course: Edward L. Bortz, Director. Welcome by Mr. Raymond F. Hosford, Director, The Lankenau Hospital, and Mr. Alfred Putnam, President, Board of Trustees, The Lankenau Hospital

NORMAL METABOLISM: Charles H. Best, Chairman

9:15 *Carbohydrate Metabolism:* Sidney Weinhouse

9:45 *Protein Metabolism:* Francis D. W. Lukens

10:15 *Fat Metabolism:* Samuel Gurin

10:45 Refreshments and Musical Interlude*

11:15 NORMAL METABOLISM: Panel Discussion: Samuel Gurin, Moderator; William C. Stadie; Charles H. Best; Sidney Weinhouse; Francis D. W. Lukens

12:30 Intermission for Luncheon

AFTERNOON

THE PATHOLOGICAL PHYSIOLOGY OF DIABETES: Henry T. Ricketts, Chairman

*Musical interludes, Joel A. Anderson at the organ. Mr. Anderson is Assistant Professor of Music, Eastern Baptist College, St. Davids, Pa., and Director of Choral Activities, Eastern Baptist Seminary, Philadelphia, Pa.

2:00 *The Mode of Action of Insulin:* William C. Stadie
2:20 *Insulin Resistance:* Francis C. Lowell
2:40 *Secondary Consequences—Electrolyte Behavior:* J. Russell Elkinton
3:00 *Insulin Deficiency:* Charles H. Best
3:20 Refreshments and Musical Interlude

4:00 SKIN DISORDERS AND DIABETES: Clinic. Demonstration of Patient. George E. Anderson, Chairman; Minerva S. Buerk, Historian; W. Wallace Dyer, Clinician

EVENING

5:30 Social Hour
Union League Club

THURSDAY MORNING, JANUARY 20

THE YOUNG DIABETIC: A. Lawrence Chute, Chairman

9:00 *General Therapy: Objectives and Standards* Priscilla White
9:30 *Laboratory Procedures:* George M. Guest
10:00 *Ketosis:* Reed Harwood
10:30 *Psychologic Problems:* William B. Kennedy
11:00 Refreshments and Musical Interlude

11:20 THE YOUNG DIABETIC: Panel Discussion. Priscilla White, Moderator; George M. Guest; Reed Harwood; William B. Kennedy
12:30 Intermission for Luncheon

AFTERNOON

OBESITY: Howard F. Root, Chairman

2:00 *Experimental Obesity:* John R. Brobeck
2:25 *Obesity and Diabetes:* Herbert Pollack
2:50 *Teaching the Doctor the Patient's Diet:* Deaconess Maude A. Behrman
3:20 *The Octogenarian Diabetic:* Howard F. Root
3:45 Refreshments and Musical Interlude

4:00 GROUP THERAPY FOR OBESITY: Clinic. E. Perry McCullagh, Chairman; Thomas E. Pilla, Historian; Joseph T. Beardwood, Jr., Clinician

EVENING

6:00 Social Hour (by subscription)
The Bellevue-Stratford
Foyer, Burgundy Room
7:00 Dinner
Burgundy Room
Entertainment: Music and Stories
Frederick W. Williams, Toastmaster

FRIDAY MORNING, JANUARY 21

THE STATUS OF COMPLICATIONS: Frank N. Allan, Chairman

9:00 *The Eye:* H. Walter Forster, Jr.
9:30 *The Peripheral Vessels:* Hugh Montgomery
10:00 *The Surgical Diabetic Patient:* Stanley I. Spoont
10:30 Refreshments and Musical Interlude
10:45 *Infections:* Henry F. Page, Jr.
11:15 *Minor Complications:* Charles R. Shuman
11:45 *General Summary:* Garfield G. Duncan
12:30 Intermission for Luncheon

AFTERNOON

2:00 STRESS AND DIABETES: Clinic. Demonstration of Patient. Edward S. Dillon, Chairman; Walter M. Bortz, II, Historian; Edward L. Bortz, Clinician
3:30—5:30 THE NATURAL HISTORY AND IDENTIFICATION OF DIABETES: Forum. Henry B. Mulholland, Moderator. Panel selected from the audience

EVENING

OPEN FORUM (Public Meeting). Auspices of Philadelphia Metabolic Association

8:00 Musical Concert, Eastern Baptist College (St. Davids, Pa.) Choir. Mr. Joel A. Anderson, Director
8:30 *Address of Welcome:* Henry B. Mulholland, President, American Diabetes Association

Panel Discussion: George P. Rouse, Jr., Moderator; Charles H. Best; Arthur R. Colwell; Robert L. Jackson; Randall G. Sprague

Selected Musical Numbers by the Choir

Presentation of J. Howard Reber Medal for Distinguished Service to Charles H. Best, by Joseph T. Beardwood, Jr., Chairman, Executive Committee, Philadelphia Metabolic Association

TOUR OF THE NEW LANKENAU HOSPITAL RESEARCH INSTITUTE

For those desiring to see the new Lankenau Hospital Research Institute, a special tour will be arranged. The following results and experiments will be in progress:

1. The chemistry of chromosomes and genes, using mainly Drosophila melanogaster as the test object.
2. Results, technics and experiments in progress assessing the role of the nuclei versus cytoplasm in differentiation. The transplantation of nuclei, using frog eggs and embryos as test objects.
3. Chromosomal content of the axcites tumors in mice and their relationship to transplantability, histocompatability, etc.
4. Fungi and their relationship to disease.
5. The folic acid-like substances of the blood.
6. The physiological chemistry of liver proteins.
7. Various facets of "intermediary metabolism of proteins, carbohydrates and fats."
8. The interconversion of chemical compounds, especially amino acids, in studies of nutrition.
9. The synthesis of protein carcinogen moieties and their biological properties.
10. Modifications of polysaccharides as used in cancer chemotherapy trials.
11. The molecular structure of biologically important compounds as studied by x-ray crystallographic technics.

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DELEGATES TO THE NATIONAL HEALTH COUNCIL
Alexander Marble, Herbert Pollack, J. Richard Connelly

Winner of the Second Medical Student and Intern Essay Contest

The Editorial Board of DIABETES takes great pleasure in announcing the selection of Dermot J. Demis, of Yale University School of Medicine, New Haven, Conn., as the winner of the 1954 award for the best paper in the field of diabetes by medical students and interns. Among papers reviewed by the Board, "Studies on a Possible Mechanism of Action of Insulin," by Dr. Demis, was chosen as the outstanding contribution.

Dr. Demis attended Stuyvesant High School (New York City), entered Union College (Schenectady, N.Y.) in 1947, and received a B.S. degree in 1950. Chemistry was his major subject. He did graduate work at the University of Rochester (Rochester, N.Y.) from 1950 to 1953, when he entered Yale Medical School. He received a Ph.D. degree from the University of Rochester in June 1954. Demis is 25 years old, married, and has a five-month-old daughter.

DERMOT J. DEMIS

As announced in previous issues of the Journal, the award of $250 was made possible through the generosity of the St. Louis Diabetes Association.

Excellent papers were submitted in this year's competition, honorable mention going to five additional authors, who were awarded a one-year subscription to DIABETES, for Volume 3, 1954. Their names and the titles of their papers follow:

Solomon E. Barr, Washington, D. C., submitted a paper entitled "Diabetes Affecting Pregnancy." Now serving his internship at the Philadelphia General Hospital, he attended George Washington University Medical School, graduating first in his class in June 1954.

Miles A. Galin, Brooklyn, N. Y., was awarded honorable mention for "A Study of the Method of Action of Sodium Diethyldithiocarbamate, a Supposed Alpha Cell Toxin." This study into the mechanisms of the alpha cell took more than two years to complete, and was carried out under the guidance of Drs. Irving Rudolph and Harold Fink, pathologists, at the Coney Island Hospital in Brooklyn. For the first year of the enterprise, Galin worked alone, but during the second year was associated with a fellow-student, Martin Reisman. Galin, a graduate of the Washington Square College of New York University, and Reisman, a graduate of Rutgers University, are both senior students at the New York University College of Medicine. Galin received the Peoples' Hospital Research Award to enable him to do this study, and Mr. Reisman was awarded a grant from the college. They are both interested in the problems of diabetes, and plan to continue their studies of the subject.

Donald W. Ortmeyer, M.D., Des Moines, Ia., is serving his internship at Broadlawns Polk County Hospital (General) in Des Moines. He is a graduate of the State University of Iowa, where he worked as a research assistant in the Department of Pediatrics under the direction of Dr. Robert L. Jackson. Dr. Ortmeyer served in the U. S. Navy from 1944 through 1946, one and one-half years of it in the Philippine Islands. His paper is entitled "Mortality Study of Young Diabetic Patients."

Fred C. Schnibbe, M.D., now serving an internship at the Portland Sanitarium and Hospital in Portland, Ore., wrote "Level of Control vs. Degenerative Complications in Juvenile Diabetes." Dr. Schnibbe is a June 1954 graduate of the School of Medicine of the College of Medical Evangelists. He served thirty months active duty with the Armed Forces during World War II, eighteen months of which was spent in Europe. He received a B.A. degree from Walla Walla College, College Place, Washington, in June 1950. Dr. Schnibbe at present plans to become a general practitioner.

James R. Stabenau, Milwaukee, Wis., wrote on "Late Complications of Diabetes Mellitus." At present a senior student at Marquette University School of Medicine, he received a B.S. degree, magna cum laude, from Marquette University in 1952. During the summer of 1953, he worked as a research assistant under Dr. J. J. Smith in the Department of Physiology, studying the relationship of hepatic anoxia to the development of secondary shock. He is a member of Alpha Omega Alpha and a contributing writer of articles for the *Marquette Medical Review*. Stabenau plans to enter the field of internal medicine.

The Editor and the Editorial Board, on behalf of the Association, offer their congratulations to Dr. Demis and those who received honorable mention.

Members of the American Diabetes Association and subscribers to DIABETES are reminded that there is a third contest closing May 10, 1955, open to medical students and physicians within two years after graduation from medical school. They are asked to urge their students and interns to submit papers by that date. Candidates may choose any subject relating to diabetes and basic metabolic problems. The length of the paper may be from six to eighteen pages, typewritten and double-spaced. Manuscripts should be sent to the Editorial Office of DIABETES, 1 East 45th Street, New York 17, N. Y. The papers will be reviewed by the Editorial Board which, in selecting the best paper, will take into consideration the value of the material and the method of presentation. The prize of $250 for the best paper reporting original work, whether laboratory investigation or clinical observations, is made possible again through the kindness of the St. Louis Diabetes Association.

An additional award of $50 for the best review article or case report has been added to this annual competition sponsored by the American Diabetes Association. It has been given anonymously by a member of the Association.

THE FIFTEENTH ANNUAL MEETING

As announced in the July-August issue of DIABETES, the next Annual Meeting of the American Diabetes Association will be held June 4-5, 1955, in Atlantic City, N. J. The meeting immediately precedes the annual session of the American Medical Association, June 6-10.

Chalfonte-Haddon Hall will again serve as headquarters for our Association. Although there is no guarantee that all of our members can be housed in the headquarters hotel, every effort will be made to accommodate them. Reservation information is going forward to the membership.

Scientific Sessions

Physicians and other scientists are invited by Frederick W. Williams, M.D., Chairman of the Association's Committee on Scientific Programs, to submit abstracts of papers which they would like to present at the Scientific Sessions.

Persons interested are requested to submit eight copies of the abstracts to facilitate review of their material by the Committee.

U. S. PUBLIC HEALTH SERVICE COURSES IN DIABETES

The Public Health Service for the fourth year is sponsoring courses in diabetes control designed for physicians, public health administrators, nurses, dietitians, nutritionists, health educators, medical technologists, and medical social workers. The courses, which are free, are conducted at the Diabetes Field Research and Training Unit, Boston, Mass. The staff includes a medical officer, internist, nutritionist, public health nurse, statistician, biochemist, health educator, and medical technicians. The group discusses the problems involved in the care of the person with diabetes in the hospital and in the community. Each course, conducted for one week, consists of discussions, demonstrations and field trips. Opportunities are provided for individual consultation.

Courses to be given during 1955 include: Patient Education in Diabetes (March 21-25; and June 6-10), Nursing Aspects of a Diabetes Program (April 11-15), Nutritional Aspects of a Diabetes Program (May 9-13), Laboratory Aspects of a Diabetes Program (upon request throughout the year), and Organization and Management of a Diabetes Clinic (upon request throughout the year). Further information may be obtained from the U. S. Public Health Service, Diabetes Field Research and Training Unit, 639 Huntington Avenue, Boston 15, Mass.

SECOND CONGRESS OF THE INTERNATIONAL DIABETES FEDERATION

Cambridge, England, will be the site of the Second Congress of the International Diabetes Federation, July 4-8, 1955. The Honorary President will be Sir Lionel Whitby, C.V.O., M.D., Master of Downing College, Cambridge.

The British Diabetic Association, 152, Harley Street, London, W.1, will act as host. Information about reservations and so forth may be secured from Mr. James G. L. Jackson of that Association, or from the National Office of the American Diabetes Association.

New Members

The following Active Members were elected as of September 1 and October 1, 1954:

Arkansas	
Robinson, Guy U.	Dumas
Connecticut	
Deren, M. David	Bridgeport
Louisiana	
Pickell, Frank W.	Baton Rouge
Massachusetts	
McAuliffe, Eugene F.	Milton
Minnesota	
Paris, Jaime I.	Rochester
New York	
deLalla, Vincent, Jr.	Utica
North Carolina	
Koury, George Eli	Burlington
Ohio	
Mendelson, Louis H.	Springfield
Pennsylvania	
Fusia, Donald A., Jr.	New Kensington
Hoover, Philip A.	Dallastown
South Carolina	
Wells, James L.	Orangeburg
Tennessee	
Nichols, Ralph G.	Knoxville
Wisconsin	
Hutter, Adolph M.	Fond du Lac
Liebman, Albert	Milwaukee

OTHER COUNTRIES

Argentina	
Campagnoli, Mario	Buenos Aires
Nusimovich, Bernardo	Santa Fe
Denmark	
Ditzel, Jörn	Copenhagen
France	
Pathe, Georges T.	Grasse

The following Associate Member was elected as of September 1, 1954:

California	
Hill, Margaret E.	Orange

News of Affiliate Associations

The 37 Affiliate Diabetes Associations throughout the United States are actively carrying out the first objective of the American Diabetes Association, namely, professional education. Either as Affiliates or through their component Clinical Societies, these local organizations are effectively disseminating scientific information about diabetes and its related problems.

Since the present Affiliate Associations cover well over half of the geographical area of the country and considerably more than half the numerical population, membership and active participation are available to the majority of physicians throughout the country. Members of the national organization and subscribers to this journal are urged to join their local group. Inquiries should be directed to the Affiliates as listed below:

CALIFORNIA

Fresno County Diabetes Association, Inc.
1915 Thorne Avenue
Fresno 5
Leo Goodman, M.D., President

Los Angeles Diabetes Association, Inc.
1680 North Vine Street
Hollywood 28
Lorenz M. Waller, M.D., Secretary-Treasurer

San Diego Diabetes Association, Inc.
2290 Sixth Avenue
San Diego
Harold C. Torbert, M.D., Secretary-Treasurer

COLORADO

Colorado Diabetes Association, Inc.
1100 E. 18th Avenue
Denver 2
Robert F. Berris, M.D., Secretary-Treasurer

CONNECTICUT

Connecticut Diabetes Association, Inc.
165 Capitol Avenue, Room 337
Hartford 15
James C. Hart, M.D., Secretary-Treasurer

DISTRICT OF COLUMBIA

Diabetes Association of the District of Columbia, Inc.
915-19 Street, N.W.
Washington 6, D.C.
William Kurstin, M.D., President

FLORIDA

Duval County Diabetes Association, Inc.
962 Main Street
Jacksonville 2
Edward R. Smith, M.D., Secretary

Miami Diabetes Association, Inc.
Suite 602, 550 Brickell Avenue
Miami 32
Carlos P. Lamar, M.D., President

GEORGIA

Diabetes Association of Atlanta, Inc.
875 W. Peachtree Street, N.W.
Atlanta 3
L. Harvey Hamff, M.D., President

ILLINOIS

Chicago Diabetes Association, Inc.
8 South Michigan Avenue
Chicago 3
Jerome T. Paul, M.D., Secretary

INDIANA

Indianapolis Diabetes Association, Inc.
410 Hume Mansur Building
Indianapolis 4
William M. Dugan, M.D., President

IOWA

See Nebraska

KANSAS

See Kansas City, Missouri

LOUISIANA

Diabetes Association of Louisiana, Inc.
1130 Louisiana Avenue
Shreveport 7
A. A. Herold, Sr., M.D., President

MAINE

See Massachusetts

MASSACHUSETTS

New England Diabetes Association, Inc.
1180 Beacon Street
Brookline 46
C. Cabell Bailey, M.D., Secretary

MICHIGAN

Michigan Diabetes Association, Inc.
3825 Brush Street
Detroit 1
Mary M. Harrington, Secretary-Treasurer

MISSOURI

Kansas City Clinical Diabetes Association, Inc.
Diabetes Lay Society of Greater Kansas City
924 Professional Building, Kansas City
Donald R. Black, M.D., President

St. Louis Diabetes Association, Inc.
3839 Lindell Boulevard
St. Louis 8
William H. Olmsted, M.D., Secretary

NEBRASKA

West Central Diabetes Association, Inc.
908 Medical Arts Building
Omaha 2
Morris Margolin, M.D., Executive Secretary

NEW HAMPSHIRE

See Massachusetts

NEW JERSEY

New Jersey Diabetes Association, Inc.
37 Randolph Place
Newark 8
Joseph Skwirsky, M.D., President, Clinical Society

NEW YORK

New York Diabetes Association, Inc.
2 East 103rd Street
New York 29
Herbert Pollack, M.D., President

Northeastern New York Diabetes Association, Inc.
46 Cornelia Street
Plattsburg
Leonard J. Schiff, M.D., Secretary-Treasurer

Rochester Regional Diabetes Association, Inc.
388 Monroe Avenue
Rochester
John R. Williams, Jr., M.D., President

NORTH DAKOTA

North Dakota Diabetes Association, Inc.
Bismarck
P. Roy Gregware, M.D., President

OHIO

Diabetes Council, Public Health Federation
222 Lafayette Circle
Cincinnati 20
Charles Maertz, M.D., Secretary

Diabetes Association of Greater Cleveland, Inc.
1465 East 55th Street
Cleveland 3
Mrs. Mary P. Wheeler, Executive Secretary

Toledo Diabetes Association, Inc.
Toledo Diabetes League
206 Michigan Street
Toledo
Howard E. Smith, M.D., President

OKLAHOMA

Oklahoma Diabetes Association, Inc.
301 N.W. 12th Street
Oklahoma City
Robert C. Lawson, M.D., Secretary-Treasurer

PENNSYLVANIA

Lehigh Valley Diabetes Association, Inc.
37 N. 3rd Street
Easton
William F. Hanisek, M.D., President

Philadelphia Metabolic Association, Inc.
1530 Spruce Street
Philadelphia 2
Miss Clara Woodward, Executive Secretary

Pittsburgh Diabetes Association, Inc.
540 Medical Arts Building
Pittsburgh 13
L. Lewis Pennock, M.D., Secretary-Treasurer

RHODE ISLAND

See Massachusetts

SOUTH DAKOTA

See Nebraska

TENNESSEE

Tennessee Diabetes Association, Inc.
188 South Bellevue
Memphis 4
Jean M. Hawkes, M.D., Secretary-Treasurer

TEXAS

Texas Diabetes Association, Inc.
1216 Main Street
Houston 1
Hugo T. Engelhardt, M.D., Secretary-Treasurer

Dallas Diabetes Association, Inc.
3622 Fairmount
Dallas 4
Edwin L. Rippy, M.D., Adviser, Clinical Society

Houston Area Diabetes Association, Inc.
3701 Montrose Boulevard
Houston
John G. Hull, M.D., President, Clinical Society

VERMONT

See Massachusetts

VIRGINIA

Virginia Diabetes Association, Inc.
Veterans Adm. Center
Kecoughtan
James F. Conner, M.D., Secretary-Treasurer

WASHINGTON

Washington Diabetes Association, Inc.
1109 Ninth Avenue
Seattle 1
Robert L. Reeves, M.D., Secretary, Clinical Society

WEST VIRGINIA

West Virginia Diabetes Association, Inc.
1212 Market Street
Parkersburg
John H. Gile, M.D., President

WISCONSIN

Wisconsin Diabetes Association, Inc.
1411 Wauwatosa Avenue
Wauwatosa 13
Karl Beck, M.D., Secretary-Treasurer

WYOMING

See Nebraska

The NEW JERSEY DIABETES ASSOCIATION is offering the J. Fred Johnson Award of $150.00 for the best essay submitted concerning diabetes mellitus.

The competing essays may cover either clinical or research investigations. They may include original studies or unusual case reports. The presentation should not exceed 3000 words. A double-spaced typewritten copy, in duplicate, must reach the Chairman of the Award Committee at 91 Lincoln Park, Newark, N. J., not later than June 1955.

Candidates are restricted to residents or internes in accredited New Jersey hospitals, or to New Jersey physicians in practice no longer than five years. The Committee which will review the manuscripts includes Selma Weiss, M.D., Chairman; William Nyiri, M.D., and Benjamin Saslow, M.D.

A place will be reserved on the program of the Metabolic Section of the Medical Society of New Jersey at its annual meeting for the presentation of the winning Prize Award Essay by the author and it will be recommended for publication in the Journal of the Medical Society of New Jersey or another appropriate journal.

This Award was made possible through the generosity of the late J. Fred Johnson who wished to stimulate the interest of young physicians in this ailment.

The WEST VIRGINIA DIABETES ASSOCIATION elected these officers in August: John H. Gile, M.D., President; J. Paul Aliff, M.D., Vice President; Delmer J. Brown, M.D., Secretary-Treasurer; Mrs. Alan Arthur, Executive Secretary. Committee Chairmen include: J. Paul Aliff, M.D., Detection and Education; George P. Heffner,

M.D., Finance; Richard N. O'Dell, M.D., Camps; Oliver H. Brundage, M.D., Program. The Lay Society (Charleston Diabetes Association) elected the following officers in October: Mrs. L. Paige Snyder, President; W. S. Engle, Vice President; Mrs. Alan J. Arthur, Secretary; P. H. Fitzgerald, Treasurer.

News Notes

Applications for Research Grants

The study section for the Institute of Arthritis and Metabolic Diseases of the Public Health Service has met to consider applications for research grants and aid. Endorsement of grant applications will be considered by the Advisory Council to the Institute on November 5 and 6.

The Public Health Service recently announced approval of 1,442 grants for assistance of medical research, aggregating $14,685,671. Fewer than one-third of the awards (459) are for new projects ($4,568,073), the remainder being for support of investigations already under way. Researchers in 335 hospitals, clinics, medical and dental schools and other institutions are grantees. Awards which will be administered by components of the National Institutes of Health include 66 new grants ($629,271) and 146 continuations ($1,375,263) for arthritis and metabolic diseases.

First Interstate Scientific Assembly at Washington, D.C.

A number of members of the Association will participate in the first Interstate Scientific Assembly sponsored by The Medical Society of the District of Columbia and The Medical Society of Virginia November 1-3, at Washington, D.C. James M. Moss, M.D., Washington, D.C., will display an exhibit, "The Symptoms of Diabetes Mellitus," in the scientific exhibit, and E. Clarence Rice, M.D., one of the exhibitors from Children's Hospital of the District of Columbia, will display an exhibit called "Staphylococcal Enteritis Following Use of Broad Spectrum Antibiotics." He is also one of the exhibitors of "Advances in the Treatment of Leukemia in Children." Alexander Marble, M.D., of Boston, will speak November 1 on "Lente Insulin in the Treatment of Diabetes."

New Hospital for Chronic Diseases in Boston

The Massachusetts Department of Health has announced the opening of the Lemuel Shattuck Hospital for chronic diseases in Boston. This hospital has a bed capacity of 600 and will have a large outpatient clinic. It is designed for the medical and surgical care of patients with chronic diseases and will serve as a nucleus for the development of prevention, teaching and research in these diseases.

To meet the admission requirements, a patient must be suffering from a chronic illness that can be helped by medical or surgical treatment, and he must be capable of rehabilitation. The total charges, when paid by the patient, range up to $7.50 per day. For outpatient examination, there is no charge; for outpatient, medical and surgical treatment, a charge of $3 per treatment is made.

Patients will not be accepted for custodial, domiciliary or terminal care, but the intent is to hospitalize those patients with chronic diseases including cancer early so that the development of the progress of these diseases may be controlled and the economic usefulness of the individuals retained. Upon completion of hospitalization, the patients will be referred back to their own physicians, other institutions or outpatient clinics, including the hospital's own outpatient department.

37th Annual Meeting of the American Dietetic Association

The American Dietetic Association held its 37th Annual Meeting at the Commercial Museum in Philadelphia October 26-29. Members of the American Diabetes Association who participated in the program and their subjects included: Waldo E. Nelson, M.D., Philadelphia: "Dietetic Management of Diabetic Children"; and Henry T. Ricketts, M.D., Chicago: "Serum Lipids and Atherosclerosis in Diabetes."

Personals

Thomas J. Coogan, M.D., Chicago; Robert L. Jackson, M.D., Columbia, Mo.; Henry T. Ricketts, M.D., Chicago; and Elmer L. Sevringhaus, M.D., Nutley, N.J., took part in the Mississippi Valley Medical Society Meeting held in Chicago September 22-24. Dr. Coogan presented a "Panel on Hypertension"; Dr. Jackson, "Care of the Child with Diabetes Mellitus"; Dr. Ricketts, "Common Problems in the Management of Diabetes Mellitus"; and Dr. Sevringhaus moderated a panel on recent developments in endocrinology.

W. Stanley Hartroft, M.D., has left the University of Toronto to accept an appointment as Professor of Pathology and Pathologist-in-Chief of Barnes Hospital at

Washington University School of Medicine in St. Louis, Mo. His new appointment began September 1.

Prof. Bernardo Houssay, Buenos Aires, Argentina, was a lecturer at the International Congress of Gynaecology and Obstetrics, held at Geneva, Switzerland, July 26-31.

Norman Jolliffe, M.D., director, bureau of nutrition, New York City Department of Health, has been named a member of a committee to study the principles which should govern the use of artificial sweeteners in foods for special dietary purposes. The committee was named by the Food and Nutrition Board of the National Research Council at the request of the Food and Drug Administration.

Prof. E. Jorpes, Stockholm, Sweden, presented "A Century of Research in Blood Coagulation," "Die Unzuverlässigkeit der Methoden zur Bestimmung der Heparinwirkung," at the International Conference on Thrombosis and Embolism at Basle, Switzerland, held July 20-24.

Robert F. Loeb, M.D., will be Presiding Chairman January 19, when D. Ewen Cameron, M.D., speaks on "Life is for Living" in the Lectures to the Laity—Twentieth Series—1954-1955 presented at the New York Academy of Medicine. The Series is entitled "Medicine in the Changing Panorama of Science."

Elaine P. Ralli, M.D., New York University, was awarded a $12,000 grant by the National Vitamin Foundation for studies on the influence of nutritional and hormonal factors in patients with diabetes mellitus.

Elmer L. Sevringhaus, M.D., Nutley, N. J., has been appointed a sectional chairman for 1954-55 by the American Drug Manufacturers Association.

Among the members of the American Diabetes Association who recently received Life Membership in the American College of Physicians are: Beeckman J. Delatour, M.D., Cassius H. Hofrichter, M.D., Burdette J. Buck, M.D., and Alex M. Burgess, Jr., M.D.

Obituaries

Christian Kevin C. Hoyle, M.D., formerly of Portsmouth, N. H., and recently of the Veterans Administration Hospital, Swannanoa, N. C., died recently at the age of 49. Dr. Hoyle was a Member of Staff of Portsmouth Hospital, Portsmouth, N. H., and a Member of Staff of the Veterans Administration Hospital, Swannanoa Division, Oteen, N.C. He served in the United States Navy Jan. 3, 1941, to Oct. 1, 1946, in the Pacific area; and was Commander (MC) in the U.S.N.R. training program, Asheville, N. C. He was a member of Alpha Omega Alpha (University of Virginia), and of Roanoke Academy of Medicine.

Virgil Frank Neumann, M.D., died suddenly Sept. 1, 1954, on the same day he assumed his new duties as Medical Director of the American Legion Hospital at Battle Creek, Mich. Dr. Neumann, formerly Senior Tuberculosis Physician at Cresson State Sanatorium, Cresson, Pa., had served on the Staff of the Saginaw County Hospital, Saginaw, Mich., from Aug. 15, 1953, until Aug. 31, 1954, when he left to assume his new position. Dr. Neumann was a graduate of the University of Michigan Medical School; he served an internship at Henry Ford Hospital in Detroit, and a residency at the Herman Kiefer Hospital in Detroit. He had also been Senior Resident Physician at Norwich State Tuberculosis Sanatorium, Norwich, Conn. He was a member of the American College of Chest Physicians and an Associate of the American College of Physicians. Dr. Neumann limited his practice to tuberculosis and diabetes. He was unmarried.